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THE AMERICAN REVIEW OF TUBERCULOSIS

A Journal of Pulmonary Diseases

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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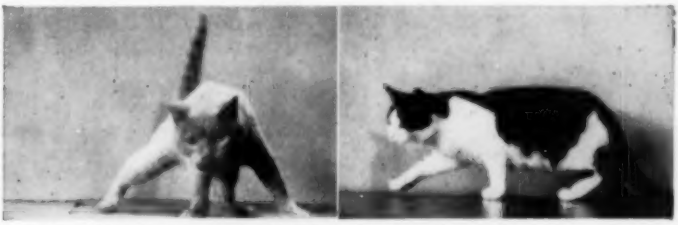

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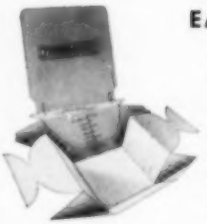

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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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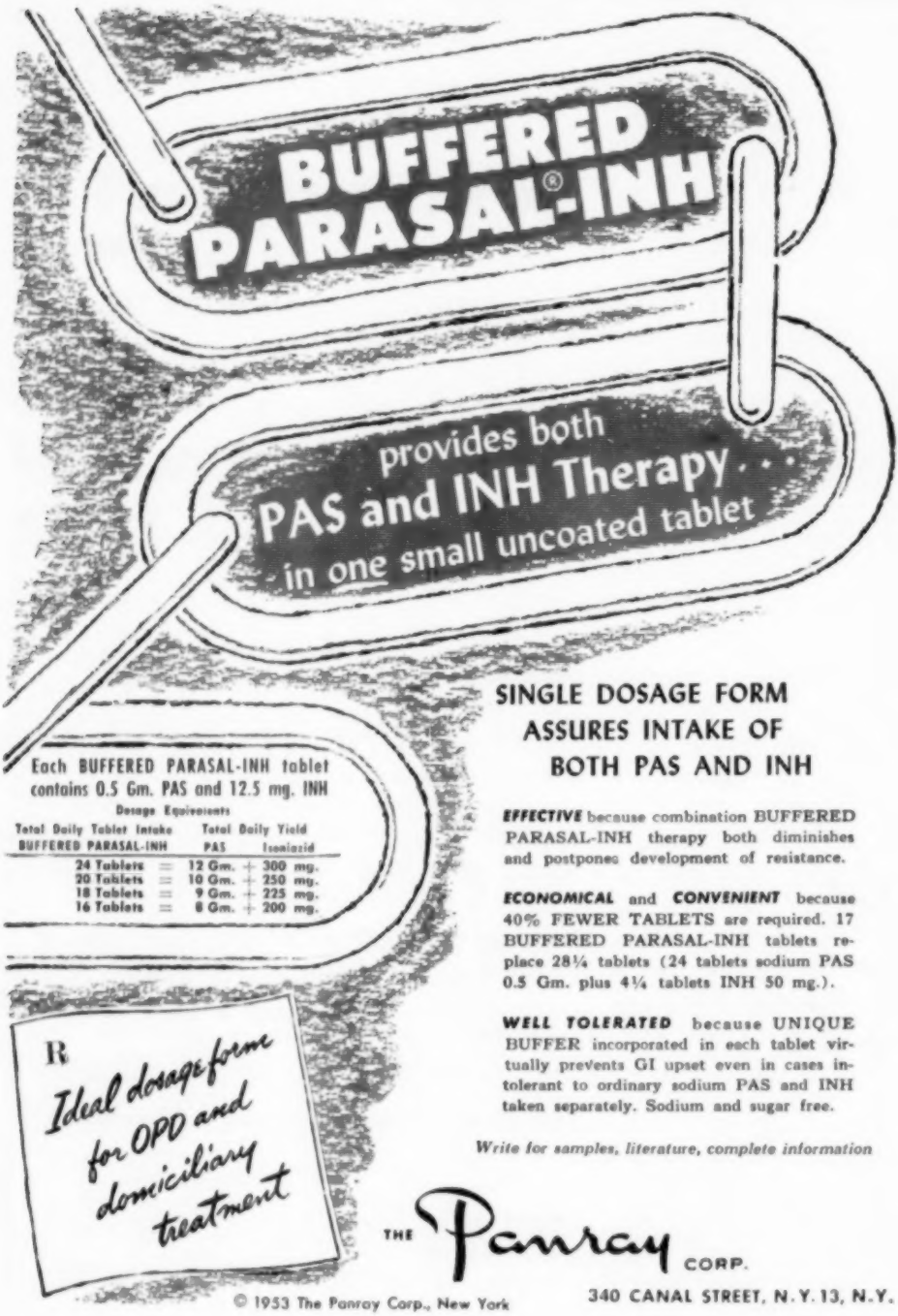

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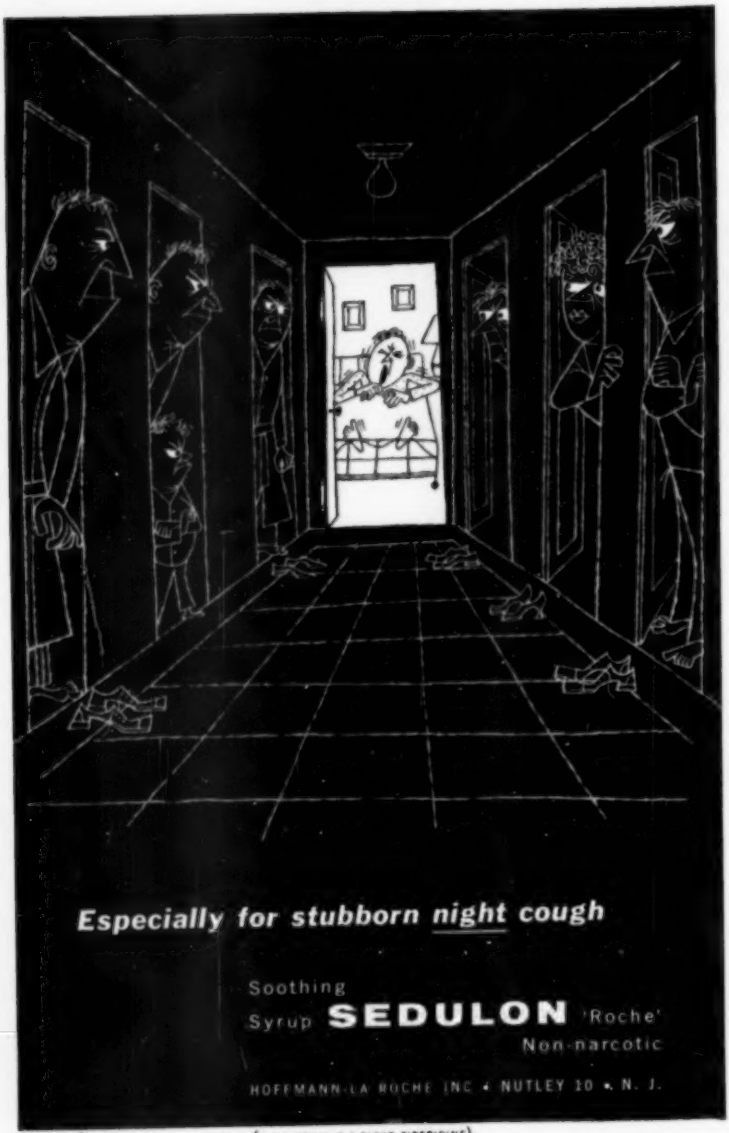

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PROGRESS REPORT ON THERAPEUTIC AND TOXIC EFFECTS OF COMBINATIONS OF ISONIAZID, STREPTOMYCIN, AND PARA-AMINOSALICYLIC ACID

United States Public Health Service Cooperative Investigation of Antimicrobial Therapy of Tuberculosis[1]

(Received for publication October 19, 1953)

INTRODUCTION

In the first of the Public Health Service studies of isoniazid in the treatment of pulmonary tuberculosis, physicians in twenty-two hospitals throughout the country treated 1,500 patients for forty weeks: one-third with 3 to 5 mg. per kg. of isoniazid daily, one-third with that dose of isoniazid plus streptomycin, and one-third with streptomycin plus para-aminosalicylic acid (PAS). Under rigidly controlled test conditions, isoniazid alone was approximately equal to streptomycin plus PAS, while the combination of isoniazid plus streptomycin was slightly superior to both. Throughout treatment, more patients who received isoniazid plus streptomycin showed clinical and roentgenographic improvement and appreciably fewer continued to produce sputum positive for tubercle bacilli.

[1] Report prepared by Shirley H. Ferebee and Dr. Frank W. Mount, and presented by Dr. Harold G. Curtis on October 15, 1953, at the Mississippi Valley Conference on Tuberculosis, Minneapolis, Minnesota; by Dr. Alfred Goldman on November 18, 1953, at the St. Louis Society of Internal Medicine, St. Louis, Missouri; and by Dr. H. M. Payne on November 10, 1953, before the Medical Society of Puerto Rico, San Juan, Puerto Rico, for the following clinical investigators: Drs. F. H. Alley, E. P. Bowerman, and S. C. Carter, Tennessee State Tuberculosis sanatoriums at Memphis and Oakville, Tenn.; Dr. C. A. Brasher, Missouri State Sanatorium, Mount Vernon, Mo.; Dr. P. T. Chapman, Herman Kiefer Hospital, Detroit, Mich.; Dr. S. S. Cohen, Glen Lake Sanatorium, Oak Terrace, Minn.; Dr. R. F. Corpe, Battey State Hospital, Rome, Ga.; Dr. Harold G. Curtis, Sunny Acres Tuberculosis Hospital, Cleveland, Ohio; Dr. R. J. Davies, Firland Sanatorium, Seattle, Wash.; Drs. Alfred Goldman, Bernard Friedman, and M. B. Pianetto, Robert Koch Hospital, Koch, Mo.; Drs. W. L. Howard and W. J. Steininger, Maybury Sanatorium, Northville, Mich.; Dr. G. E. Martin, Pittsburgh Tuberculosis Hospital, Pittsburgh, Pa.; Dr. H. M. Payne, Freedmen's Hospital, Washington, D. C.; Dr. R. F. Payne, Eugene Talmadge Memorial Hospital, Augusta, Ga.; Drs. H. C. Sweany, B. L. Brock, A. M. Dietrich, and W. L. Potts, Florida State sanatoriums at Orlando, Tampa, and Lantana, Fla.; Drs. H. S. Willis, H. F. Easom, W. H. Gentry, and C. D. Thomas, North Carolina State sanatoriums at Wilson, McCain, and Black Mountain, N. C.; Dr. G. C. Wilson, Uncas-on-Thames Sanatorium, Norwich, Conn.; Dr. J. E. Wilson, USPHS Hospital, Brooklyn, N. Y.; and Drs. J. L. Wilson, H. C. Dooling, G. M. Eckley, and H. W. Weest, Pennsylvania State sanatoriums at South Mountain, Cresson, and Hamburg, Pa.

Problems created by the appearance of drug-resistant organisms must, however, also be considered in an over-all appraisal of the three regimens. Tubercle bacilli found in patients who *still produce "positive" sputum* almost invariably become drug resistant—to streptomycin when streptomycin and PAS are given, to isoniazid when only isoniazid is given, and to both streptomycin and isoniazid when both drugs are given. The clinical superiority of the regimen containing both streptomycin and isoniazid must, therefore, be weighed against the possible disadvantages of encouraging the appearance of strains of tubercle bacilli resistant to both of the principal antituberculous drugs. A next step in advancing tuberculosis chemotherapy appeared to be, therefore, to find a regimen as effective as streptomycin plus isoniazid but one which would not result in strains of bacilli resistant to both drugs.

In the absence of a new drug which might meet or exceed these specifications, the possibilities seem to be limited to combinations of the three available agents, isoniazid, streptomycin, and PAS. The objective might be attained by a combination so effective that all patients would become "sputum negative" or by a combination which does not require the simultaneous use of the two most potent drugs, isoniazid and streptomycin, or by increasing the dosage of the newest agent, isoniazid.

A small investigation carried on as a part of the first study provided preliminary comparisons with two additional regimens, isoniazid plus PAS, and the combination of all three drugs, isoniazid, streptomycin, and PAS. In the pilot trial, both of the two new regimens appeared to be as effective as streptomycin plus isoniazid. The problem of bacterial resistance, however, could not be judged in such a small series of cases.

Therefore, in March of this year, the entire group of cooperating hospitals adopted a protocol for a second large-scale study which included these two regimens, as well as isoniazid plus streptomycin, the regimen which had previously showed the best results. The study is designed to compare PAS and streptomycin as partners for isoniazid, evaluate the simultaneous use of all three drugs, and determine the effect of larger doses of isoniazid.

MATERIALS AND METHODS

To obtain information on these questions, five regimens were adopted for which the drugs and daily doses are as follows:

Isoniazid (3 mg. per kg.) plus streptomycin
Isoniazid (3 mg. per kg.) plus PAS
Isoniazid (10 mg. per kg.) plus streptomycin
Isoniazid (10 mg. per kg.) plus PAS
Isoniazid (10 mg. per kg.) plus streptomycin and PAS

Streptomycin was given in dosages of 1 gm. twice a week; PAS, 10 to 12 gm. daily; and isoniazid in doses of 3 or 10 mg. per kg. daily.

Only patients with pulmonary tuberculosis who have received no previous antimicrobial therapy are eligible for this second study. After a patient has been selected for the study by a participating hospital, the drug regimen he is to receive is assigned in the central office[2]

[2] Field Research Branch, Division of Chronic Disease and Tuberculosis, Public Health Service, Department of Health, Education, and Welfare.

by a scheme of random numbers. Each patient, except in certain very unusual and well-defined situations, receives for forty weeks the antimicrobial agents specified by random allocation, and no others; and receives such other treatment as may be prescribed by his physician.

At the beginning and at four-week intervals during treatment, clinical observations are made, chest roentgenograms are obtained, and sputum specimens are examined microscopically and by culture. The reports and roentgenograms are forwarded to the central office for analysis and evaluation. Cultures are tested for susceptibility to streptomycin and to isoniazid in a single laboratory, the Trudeau Laboratory under the direction of Mr. William Steenken, *Jr.*

Experience in previous clinical trials indicated that, even though the studies are limited to patients whom the investigators believe can be kept under observation for the period prescribed by the protocol, a sizable number will leave the hospital before the completion of forty weeks of treatment. Anticipation of these losses has accentuated the need for the study of large numbers of patients. However, limitation of the case material to patients without previous chemotherapy has decreased the rate at which patients could be selected. Consequently, it has taken some months to accumulate sufficient patients for the second study. By October 15, 1953, more than 1,600 patients had been admitted but most of them have been under observation for only short periods of time.

The present paper is, therefore, in the nature of a progress report based on patients who have been observed longest in this, the second large-scale study in the isoniazid evaluation program. In mid-September, 1953, the investigators met in Washington and evaluated the roentgenographic changes in patients who had completed twenty weeks of treatment by that time. Comparable clinical and bacteriologic data have also been assembled, but the longer time required to determine drug susceptibility makes it impossible to include data on bacterial resistance in the present report.

OBSERVATIONS

Patients who did not complete twenty weeks of treatment: By early April, 1953, 461 patients had been admitted to the study and randomly assigned to the five treatment regimens: 91 to 3 mg. of isoniazid per kg. plus streptomycin, 85 to 3 mg. of isoniazid per kg. plus PAS, 95 to 10 mg. of isoniazid per kg. plus streptomycin, 102 to 10 mg. of isoniazid per kg. plus PAS, and 88 to 10 mg. of isoniazid per kg. plus streptomycin plus PAS. All of the 461 patients could, theoretically, have completed twenty weeks of treatment by early September, but by that time 126 of them (27 per cent) were no longer being treated according to the protocol. Records for approximately one-quarter of the group will not be used, therefore, to measure the therapeutic effectiveness of the assigned treatment; they can, nevertheless, furnish useful information on the relative practicability of the different regimens.

The reasons why the prescribed chemotherapy was not followed for these 126 cases are shown in table 1. Two reasons, departure from the hospital and failure to tolerate one or more of the prescribed drugs, account for 94 per cent of these cases. Only 2 patients refused treatment, one assigned to 3 mg. of isoniazid per kg. plus PAS and the other assigned to 10 mg. of isoniazid per

kg. plus streptomycin. Treatment was changed because of critical worsening in 3 patients: one receiving 3 mg. of isoniazid per kg. plus streptomycin; one, 3 mg. of isoniazid per kg. plus PAS; and one, 10 mg. of isoniazid per kg. plus PAS.

Equal proportions of patients in each regimen group could be expected to leave the hospital against advice if the probability of leaving was unrelated to the patients' attitude toward the drugs they received. The fact that these proportions are not equal suggests that the chemotherapeutic agents may influence the decision to leave or not to leave the hospital. Patients given PAS left more frequently than those given streptomycin, and the highest proportion leaving the hospital was among those who received all three drugs, as shown in

TABLE 1

PERCENTAGE DISTRIBUTION OF REASONS 126 PATIENTS ON ALL REGIMENS DID NOT COMPLETE TWENTY WEEKS OF PRESCRIBED CHEMOTHERAPY

REASON	NUMBER	PER CENT
Total	126	100.0
Left hospital	73	57.9
Drug intolerance	46	36.5
Refused treatment	2	1.6
Critical worsening	3	2.4
Nontuberculous illness	2	1.6

TABLE 2

NUMBER AND PER CENT OF PATIENTS ON EACH REGIMEN WHO LEFT THE HOSPITAL DURING THE FIRST TWENTY WEEKS OF THERAPY

REGIMEN	NUMBER	PER CENT OF ALL PATIENTS
Total	73	15.8
3 mg. of isoniazid per kg. + streptomycin	11	12.1
3 mg. of isoniazid per kg. + PAS	14	16.5
10 mg. of isoniazid per kg. + streptomycin	10	10.5
10 mg. of isoniazid per kg. + PAS	18	17.6
10 mg. of isoniazid per kg. + streptomycin + PAS	20	22.7

table 2. Increasing the dose of isoniazid does not appear to increase the probability of leaving. On regimens including isoniazid in combination with either streptomycin or PAS, patients left the hospital in about equal numbers whether the dosage of isoniazid was 3 or 10 mg. per kg.

In order to preserve the initial comparability of the treatment groups obtained by randomization, the chemotherapy assigned to a patient was not changed during the study unless continuation clearly imperiled his welfare. In addition to critical deterioration, intolerance to a prescribed antimicrobial was regarded as a sufficient reason to change chemotherapy. Because of the difficulty of establishing a cause and effect relationship between a sign of toxicity and a particular drug, it was decided to adopt the following procedure before a pa-

tient's assigned chemotherapy was changed. When toxic symptoms appeared, the suspected drug was discontinued; if symptoms then disappeared, treatment was resumed with a test dosage of the drug; only if the symptoms reappeared was the suspected drug definitely charged with producing the symptoms and chemotherapy changed.

In table 3 is shown the number of patients on each regimen who, by this definition, failed to tolerate one or more of the drugs in the regimen to which they were assigned. Drug toxicity made it necessary to change treatment for 46 patients, 11 of whom were regarded as being toxic to two drugs.

TABLE 3

NUMBER OF PATIENTS* ON EACH REGIMEN WHO FAILED TO TOLERATE ASSIGNED CHEMOTHERAPY, CLASSIFIED BY SPECIFIC DRUG INTOLERANCE

REGIMEN	INTOLERANCE TO		
	Isoniazid	Streptomycin	PAS
Total	31	7	19
3 mg. of isoniazid per kg. + streptomycin	1	1	—
3 mg. of isoniazid per kg. + PAS	1	—	5
10 mg. of isoniazid per kg. + streptomycin	9	4	—
10 mg. of isoniazid per kg. + PAS	13	—	11
10 mg. of isoniazid per kg. + streptomycin + PAS	7	2	3

* Eleven patients who were unable to tolerate two drugs are included twice.

TABLE 4

NUMBER AND PER CENT OF PATIENTS ON EACH REGIMEN WHO FAILED TO TOLERATE PRESCRIBED CHEMOTHERAPY

REGIMEN	NUMBER ASSIGNED	FAILED TO TOLERATE	
		Number	Per Cent
3 mg. of isoniazid per kg. + streptomycin	91	1	1.1
3 mg. of isoniazid per kg. + PAS	85	5	5.9
10 mg. of isoniazid per kg. + streptomycin	95	11	11.6
10 mg. of isoniazid per kg. + PAS	102	19	18.6
10 mg. of isoniazid per kg. + streptomycin + PAS	88	10	11.4

Isoniazid, at the 3 mg. per kg. dose, was toxic for only 2 patients, 1 per cent of 176 receiving this dose; and for 29 patients, more than 10 per cent of 285 receiving the 10 mg. per kg. dose. PAS toxicity appeared in 19 patients or approximately 7 per cent of the 275 patients who received the drug. Streptomycin toxicity affected 7 patients, or approximately 3 per cent, of 274 patients on streptomycin regimens.

The usefulness of any treatment is in part dependent on how well it can be tolerated. Toleration is dependent on the toxicity of the individual drugs in the dosage used. Information is given in table 4 on the extent to which patients who received the various drug combinations were unable to continue the pre-

scribed chemotherapy because they could not tolerate at least one of the drugs. Since isoniazid at the 10 mg. per kg. level was the most toxic agent and PAS was more toxic than streptomycin, it is not surprising that the regimens employing both PAS and the high dose of isoniazid should have the highest rate of intolerance: 18.6 per cent for 10 mg. of isoniazid per kg. plus PAS and 11.4 per cent for 10 mg. of isoniazid per kg. plus streptomycin plus PAS. Likewise, it is reasonable that streptomycin plus the low dose of isoniazid should have the lowest rate, 1.1 per cent.

The investigators recognized that, with the adoption of these regimens, they might be venturing into the toxic range of isoniazid and were watchful for signs of difficulty. In May, 1953, reports of the appearance of peripheral neuritis in patients who received the higher doses of isoniazid prompted an immediate review of the patients in this study. Only six of the twenty-two hospitals reported any cases of peripheral neuritis: 2 in each of three hospitals and one in each of three hospitals. These 9 patients were all on regimens of 10 mg. per kg. dosage of isoniazid, 2 receiving isoniazid with streptomycin, 3 with PAS, and 4 with both streptomycin and PAS. The neuritis occurred among a total of 268 patients who had been treated for at least twelve weeks on these three regimens, a rate of 3.4 per cent. Symptoms first appeared between the forty-second and ninety-fifth days of treatment, averaging approximately sixty-five days. Isoniazid was discontinued in 4 cases, the dosage was reduced in 2 cases, and was continued unchanged in 3 cases. At the time of writing this report, all of the 9 patients had improved or completely recovered.

Patients who completed twenty weeks of treatment: Of the 335 patients observed for the full twenty weeks, 46 per cent were white males; 28 per cent, white females; 15 per cent, Negro males; and 11 per cent, Negro females. Thirty-six per cent were less than thirty-five years of age; 44 per cent, between thirty-five and fifty-four; and 20 per cent, fifty-five years and older. Eighty-six per cent of the patients had been hospitalized for tuberculosis for the first time within the year in which the study was started, and only 14 per cent have had disease of longer duration. The disease in 5 per cent of the patients was minimal in extent, moderately advanced in 43 per cent, and far advanced in 52 per cent of the total series.

The five treatment groups are comparable with respect to these characteristics of the patients. Of the total, 78 are being treated with 3 mg. of isoniazid per kg. plus streptomycin, 64 with 3 mg. of isoniazid per kg. plus PAS, 73 with 10 mg. of isoniazid per kg. plus streptomycin, 63 with 10 mg. of isoniazid per kg. plus PAS, and 57 with 10 mg. of isoniazid per kg. plus streptomycin plus PAS.

Results

Mortality: On each regimen, except 3 mg. of isoniazid per kg. plus streptomycin, one patient died of tuberculosis during the first twenty weeks.

Bacteriologic studies: Figure 1*A* and the first section of table 5 show at four-week intervals the percentage of patients on each regimen in whose sputum tubercle bacilli were detected by microscopic examination. At the beginning of

treatment, the percentages ranged among regimens from 56 to 69. The percentage of patients with "positive" sputum smears decreased on all regimens throughout treatment. At the twentieth week, from 6 to 15 per cent of the patients on the various regimens still had "positive" smears.

The results of culture of the same specimens are available through only the sixteenth week of treatment and are reported in figure 1*B* and the second section of table 5. Although the percentage of cultures positive for *M. tuberculosis*

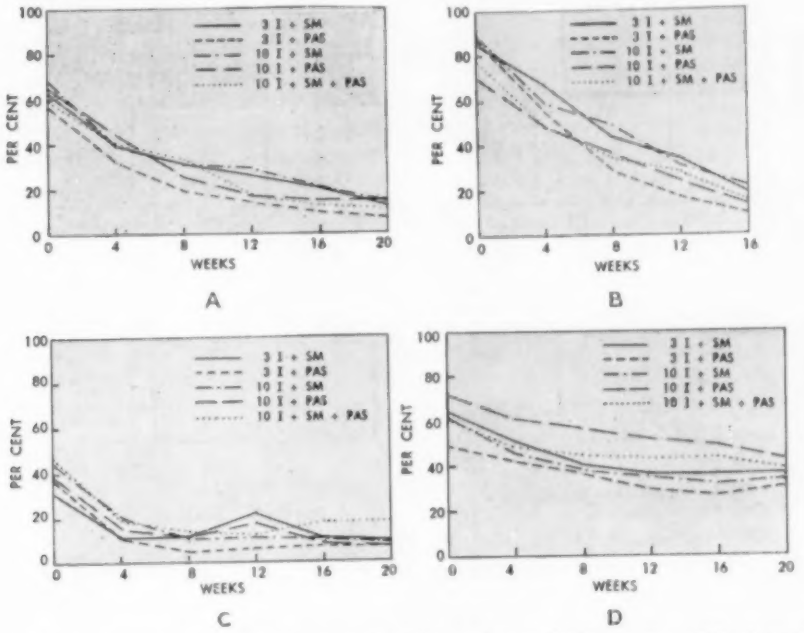

FIG. 1. Percentage of patients on each of five regimens showing unfavorable signs of their disease.

A. Percentage of patients with smear positive for tubercle bacilli.

B. Percentage of patients with culture positive for tubercle bacilli.

C. Percentage of patients with fever.

D. Percentage of patients underweight.

among patients on each regimen is higher than the corresponding percentage of positive smears, the trend is the same: continuous decrease during treatment in the proportion of patients with positive bacteriology. At the start of treatment, the percentage of patients with "positive" cultures ranged from 71 to 89 per cent, and, after sixteen weeks of treatment, from 9 to 21 per cent. The findings both on smear and on culture show no significant difference among regimens in the rate of bacteriologic change.

Course of fever: Figure 1*C* and the third section of table 5 show the proportion

TABLE 5

PROPORTION OF PATIENTS ON EACH REGIMEN IN UNFAVORABLE CLINICAL CONDITION, BY WEEK OF TREATMENT

	5 MG. OF ISONIAZID PER KG. + STREPTOMYCIN	5 MG. OF ISONIAZID PER KG. + PAS	10 MG. OF ISONIAZID PER KG. + STREPTOMYCIN	10 MG. OF ISONIAZID PER KG. + PAS	10 MG. OF ISONIAZID PER KG. + STREPTOMYCIN + PAS
Number of Cases	78	64	73	63	57
Per Cent with Sputum Positive for Tubercle Bacilli by Direct Examination					
Selection	62.8	56.3	68.5	65.1	59.7
4 weeks	38.5	31.7	38.9	44.4	40.4
8 weeks	30.8	18.7	30.2	25.4	33.3
12 weeks	25.7	14.1	29.2	17.5	17.6
16 weeks	19.5	9.4	20.6	14.3	12.3
20 weeks	11.5	6.3	13.7	14.7	10.5
Per Cent with Sputum Positive for Tubercle Bacilli by Culture					
Selection	84.9	86.7	88.7	70.5	77.8
4 weeks	67.6	55.7	59.1	48.4	48.2
8 weeks	43.4	29.0	48.6	36.7	33.9
12 weeks	33.8	16.4	30.9	23.8	27.8
16 weeks	18.1	8.6	20.9	12.9	14.9
20 weeks	NA‡	NA	NA	NA	NA
Per Cent Febrile*					
Selection	32.0	37.5	45.2	39.7	47.4
4 weeks	11.6	11.0	20.6	15.9	19.3
8 weeks	11.5	4.7	9.6	11.1	14.1
12 weeks	21.8	6.3	10.9	17.5	12.3
16 weeks	9.0	6.3	9.6	8.0	17.6
20 weeks	7.7	6.3	8.3	6.4	17.6
Per Cent Underweight†					
Selection	65.3	51.5	63.9	73.0	63.2
4 weeks	52.6	42.2	47.9	61.9	50.0
8 weeks	42.3	37.5	39.7	57.2	45.6
12 weeks	37.2	29.7	36.1	52.4	43.9
16 weeks	36.4	26.6	31.9	49.2	43.9
20 weeks	36.4	29.7	33.4	43.6	38.6

* Median of highest oral temperature for five days: febrile, 99.0°F. and over.

† Minus deviation of more than 10 per cent from standard height-weight values.

‡ Not available.

of febrile patients at each four-week interval. At the beginning of treatment, the percentage of patients with temperatures of 99.0°F. or more ranged among regimens from 32 to 47. Most of the reduction in the proportion of febrile patients occurred on all regimens during the first four weeks of treatment with little further change.

Body weight: Figure 1*D* and the fourth section of table 5 show the proportion of underweight patients on each regimen at each four-week interval. Patients were arbitrarily classified as underweight when they were more than 10 per cent below a so-called "normal" weight according to a standard height-weight chart. The 5 regimens differed more on the proportion underweight at the start of treatment than on most other characteristics: 52 per cent of those on 3 mg. of isoniazid per kg. plus PAS to 73 per cent of the group receiving 10 mg. of isoniazid per kg. plus PAS. The number of underweight patients decreased on all regimens during twenty weeks of treatment. At the twentieth week, the range between the groups was slightly less than at the beginning of treatment, from 30 per cent in the 3 mg. of isoniazid per kg. plus PAS regimen to 44 per cent in the 10 mg. of isoniazid per kg. plus PAS regimen. However, with groups of this size, it can be said only that the changes during treatment are of approximately the same order on all regimens.

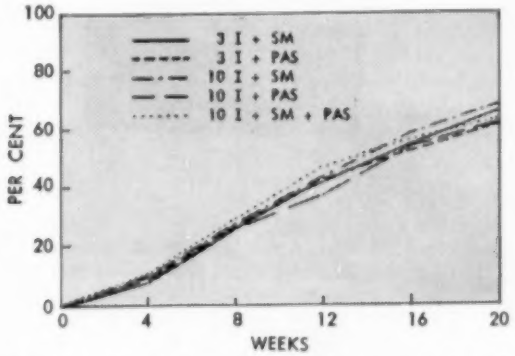

FIG. 2. Proportion of significant roentgenographic improvement in patients on five treatment regimens.

Roentgenographic changes: Roentgenographic changes in the first twenty weeks of the second study have been evaluated in exactly the same way as in the first large study of isoniazid. That is, the clinical investigators met in Washington and read all the films for each patient. Without having any information about the patients, they classified the films according to changes in the pulmonary lesions between the start of treatment and each succeeding four-week interval for twenty weeks. Roentgenographic change was classified on a 7-point scale, ranging from marked improvement to marked deterioration. The results of these readings are shown in figure 2 and table 6.

The proportion of patients showing significant (marked or moderate) roentgenographic improvement increased steadily on all regimens throughout twenty weeks of treatment. All five regimens appeared to be very effective in producing significant roentgenographic improvement. The similarity of the results on the various regimens is striking: by the end of twenty weeks of treatment, the range

TABLE 6

PERCENTAGE DISTRIBUTION OF ROENTGENOGRAPHIC CHANGE AT FOUR-WEEK INTERVALS IN 335 PATIENTS OBSERVED TWENTY WEEKS

	CHANGE FROM BEGINNING OF TREATMENT								
	Total	Improvement			No change	Deterioration			Death
		Marked	Moderate	Slight		Slight	Moderate	Marked	
3 mg. of isoniazid per kg. plus streptomycin									
4 weeks	100.0	—	7.7	35.5	54.3	0.8	1.7	—	—
8 weeks	100.0	0.4	26.5	42.3	27.8	1.7	1.3	—	—
12 weeks	100.0	3.8	38.9	36.3	18.4	1.7	0.9	—	—
16 weeks	100.0	14.9	40.2	26.9	16.7	0.9	0.4	—	—
20 weeks	100.0	24.8	41.5	22.2	10.7	0.4	0.4	—	—
3 mg. of isoniazid per kg. plus PAS									
4 weeks	100.0	0.5	9.0	43.9	42.9	2.6	1.1	—	—
8 weeks	100.0	3.7	23.3	42.8	27.0	2.1	1.1	—	—
12 weeks	100.0	6.9	37.0	29.6	22.2	3.2	1.1	—	—
16 weeks	100.0	14.7	38.4	26.9	17.4	0.5	0.5	—	1.6
20 weeks	100.0	26.0	35.9	21.9	13.0	—	1.6	—	1.6
10 mg. of isoniazid per kg. plus streptomycin									
4 weeks	100.0	—	9.8	41.9	45.5	0.9	0.5	—	1.4
8 weeks	100.0	2.4	24.6	43.4	26.4	0.9	0.9	—	1.4
12 weeks	100.0	8.7	35.3	34.9	17.4	1.8	0.5	—	1.4
16 weeks	100.0	15.2	43.8	26.3	11.0	1.4	0.9	—	1.4
20 weeks	100.0	26.3	42.8	21.2	7.3	0.5	0.5	—	1.4
10 mg. of isoniazid per kg. plus PAS									
4 weeks	100.0	0.5	9.6	39.4	47.3	1.6	—	—	1.6
8 weeks	100.0	4.3	22.0	40.3	28.0	2.7	1.1	—	1.6
12 weeks	100.0	7.5	29.9	42.2	13.9	2.7	1.1	1.1	1.6
16 weeks	100.0	13.4	41.1	29.4	11.2	1.1	1.1	1.1	1.6
20 weeks	100.0	21.9	40.4	25.5	9.0	—	1.1	0.5	1.6
10 mg. of isoniazid per kg. plus streptomycin plus PAS									
4 weeks	100.0	0.6	9.3	38.0	47.4	4.1	—	0.6	—
8 weeks	100.0	4.7	25.1	36.2	26.9	4.1	1.2	—	1.8
12 weeks	100.0	11.7	36.2	29.8	16.4	3.5	0.6	—	1.8
16 weeks	100.0	21.1	36.2	26.9	11.7	2.3	—	—	1.8
20 weeks	100.0	32.8	31.5	24.4	7.7	1.8	—	—	1.8

among regimens was between 62 and 69 per cent showing significant roentgenographic improvement.

DISCUSSION

The preliminary results of this cooperative study of antimicrobials in tuberculosis must be interpreted with caution because they are based on groups of only moderate size and on only a limited period of observation. Nevertheless, the present results make possible comparisons which will be of considerable practical importance if confirmed as the study progresses.

From the present material, several indications of the therapeutic effectiveness of combinations of the available chemotherapeutic agents appear. First, isoniazid plus PAS is as effective as isoniazid plus streptomycin. Second, this study offers no evidence that the simultaneous use of all three drugs is superior to the combination of either isoniazid plus streptomycin or isoniazid plus PAS. Third, there is no indication that therapeutic effectiveness increases with increasing dosage of isoniazid.

When all regimens tested show equal therapeutic effectiveness, differences in the frequency of toxic drug reactions assume increased importance in choosing therapy. In these preliminary findings, isoniazid given in doses of 3 mg. per kg. daily produced practically no toxicity, but one of every 10 patients who began treatment with isoniazid at the 10 mg. per kg. dosage developed toxic symptoms which necessitated a change in therapy.

If confirmed, these findings point to three conclusions: first, that isoniazid, streptomycin, and PAS should not be used simultaneously; second, that, over all, the 3 mg. per kg. daily dose of isoniazid is preferable to the 10 mg. per kg. dose since it equals the higher dose in therapeutic effectiveness and is appreciably less toxic; and third, the wisdom of wide use of the combination of isoniazid plus streptomycin may be questioned since isoniazid plus PAS is equally effective.

SUMMARY

From a study of more than 1,600 patients with pulmonary tuberculosis, a preliminary report has been prepared on the results of chemotherapy in 461 patients who have been under observation longest. By random allocation the patients were divided among five treatment regimens: 3 mg. of isoniazid per kg. plus streptomycin, 3 mg. of isoniazid per kg. plus PAS, 10 mg. of isoniazid per kg. plus streptomycin, 10 mg. of isoniazid per kg. plus PAS, and 10 mg. of isoniazid per kg. plus streptomycin plus PAS. The study was designed to compare PAS and streptomycin as partners for isoniazid, to evaluate the simultaneous use of all three drugs, and to determine the effect of increasing the dose of isoniazid.

This progress report gives information on the therapeutic and toxic effects during twenty weeks of treatment. The therapeutic effect has been measured by roentgenographic, clinical, and bacteriologic comparisons of the five regimens. The tentative results indicate: that isoniazid plus PAS is as effective as isoniazid plus streptomycin; that the simultaneous use of all three drugs is not superior to a combination of either isoniazid plus streptomycin or isoniazid plus PAS; and that, while the therapeutic effectiveness of isoniazid does not increase with increasing dosage, toxic reactions are much more frequent at the higher dose.

SUMARIO

Informe Intermedio sobre los Efectos Terapéuticos y Tóxicos de las Combinaciones de Isoniacida, Estreptomicina y Acido Para-Aminosalicílico

Basado en el estudio de más de 1,600 tuberculosos pulmonares, se ha preparado una reseña preliminar de los resultados de la quimioterapia en los 461 enfermos que han estado más tiempo en observación. Por clasificación al azar, se dividió a los enfermos entre cinco regímenes terapéuticos: 3 mg. de isoniacida por kg. de peso más estreptomicina; 3 mg. de isoniacida por kg. más PAS; 10 mg. de isoniacida por kg. más estreptomicina; 10 mg. de isoniacida por kg. más PAS; y 10 mg. de isoniacida por kg. más estreptomicina más PAS. Tenía por fin el estudio comparar el PAS y la estreptomicina como coadyuvantes de la isoniacida, justipreciar el empleo simultáneo de las tres drogas y determinar el efecto de un aumento de la dosis de isoniacida.

Este informe intermedio aporta datos acerca de los efectos terapéuticos y tóxicos observados durante veinte semanas de tratamiento. El efecto terapéutico se computó por medio de comparaciones roentgenográficas, clínicas y bacteriológicas de los cinco regímenes. Indican los resultados tentativos: que la isoniacida más PAS es tan eficaz como la isoniacida más estreptomicina; que el uso simultáneo de las tres drogas no es superior a una combinación de la isoniacida ya con estreptomicina o con PAS; y que, aunque la eficacia terapéutica de la isoniacida no aumenta al aumentar la dosis, sí son mucho más frecuentes las reacciones tóxicas con las dosis más altas.

RESUME

Rapport préliminaire sur les effets thérapeutiques et toxiques des traitements combinés avec l'isoniazide, la streptomycine et l'acide para-aminosalicylique

D'après une étude portant sur plus de 1600 malades atteints de tuberculose pulmonaire, il a été établi un rapport préliminaire sur les résultats de la chimiothérapie chez les 461 patients qui ont été le plus longtemps en observation. Les malades ont été répartis au hasard dans chacune de ces cinq catégories de traitement: 3 mg. d'isoniazide par kg. plus streptomycine; 3 mg. d'isoniazide par kg. plus PAS; 10 mg. d'isoniazide par kg. plus streptomycine; 10 mg. d'isoniazide par kg. plus streptomycine plus PAS. Cette étude avait pour but la comparaison du PAS et de la streptomycine comme adjuvants de l'isoniazide, l'évaluation de l'emploi simultané de ces trois drogues et la détermination de l'effet de l'accroissement de la dose d'isoniazide.

Ce rapport préliminaire donne des informations sur les effets thérapeutiques et toxiques au cours d'un traitement de vingt semaines. L'action thérapeutique a été mesurée en comparant ces programmes de cure du point de vue radiologique, clinique et bacétriologique. Les résultats actuels indiquent: que l'isoniazide plus le PAS est aussi efficace que l'isoniazide plus la streptomycine; que l'usage simultané des trois drogues ne donne pas de résultats supérieurs à ceux de la thérapie combinée isoniazide-streptomycine ou isoniazide-PAS et également que si l'efficacité thérapeutique de l'isoniazide n'augmente pas avec l'augmentation des doses, les réactions toxiques sont beaucoup plus fréquentes avec les doses plus fortes.

THE RESULTS OF TREATMENT OF 549 CASES OF TUBERCULOUS MENINGITIS[1]

JOHN LORBER

(Received for publication July 7, 1953)

INTRODUCTION

In the last six years, considerable experience has been gained in the treatment of tuberculous meningitis with streptomycin, and a large number of papers have appeared both in Great Britain and elsewhere dealing with various aspects of the subject. Nevertheless, there is as yet no exact knowledge about the survival rate which can be expected with streptomycin or of the condition of the survivors. The prognostic significance of the age on admission and of the stage and the type of the disease have not yet been fully determined. It is necessary to treat a really large series of patients and to observe them for a prolonged period to determine these points with statistical accuracy. In Great Britain, the Ministry of Health (1) conducted a combined investigation and reported the results obtained in 369 patients who were observed for a minimum of thirty-four months. That investigation, however, dealt only with patients who were admitted before July, 1948. At that time, experience in the treatment of tuberculous meningitis was still lacking, and improvements in the results could be expected with more experience.

In view of the development of new antituberculous drugs, it was thought advisable to present the results in a large series of cases, so as to provide an adequate basis for comparison with results to be obtained with newer techniques and other drugs or combination of drugs. No single center could provide enough cases for a statistical analysis. It was therefore decided to analyze the combined results obtained in those five large centers in England in which treatment of tuberculous meningitis was begun in 1947 and whose published results revealed an over-all survival rate of at least 40 per cent with a minimum follow-up period of one year. The centers are the Hospital for Sick Children, Great Ormond Street, London; the Whittington Hospital, London; The Radcliffe Infirmary, Oxford; the Newcastle group of hospitals; and this clinic (Sheffield).

The following kindly supplied their data from four of these centers:

Dr. I. A. B. Cathie (Hospital for Sick Children, London)
Dr. F. Robertson (Newcastle)
Dr. Honor V. Smith (Oxford)
Dr. Sulamith Wolff (Whittington Hospital, London)

The data from these four centers, together with those from this clinic (Sheffield), form the basis of the present report.

[1] From the Department of Child Health of the University of Sheffield, Sheffield, England.

MATERIAL OF THE PRESENT INVESTIGATION

The results of treatment in 549 consecutive cases of tuberculous meningitis have been analyzed. The patients were all admitted and treated between 1947 and 1950, inclusive.[2] All patients admitted to the 5 units are included in the series with the exception of those who were transferred from other hospitals after more than one month of unsuccessful treatment. Patients who died within a few hours of admission are included. The series is, therefore, unselected.

In 513 patients, tubercle bacilli were recovered from the cerebrospinal fluid during life. The remaining 36 patients were included in the series because in each case there was adequate circumstantial evidence that the diagnosis was correct. The results of treatment in these 36 were almost identical with those in the other cases. The diagnosis was confirmed in all of the 18 of these 36 patients who came to necropsy.

The number of patients treated at the different centers ranged from 72 to 146. Statistical analysis of the composition of the five separate series showed that they were comparable with regard to the stage of disease on admission and the type of disease. Three centers (Whittington, Newcastle, and Oxford) treated adults and children; the other two (Great Ormond Street and Sheffield) treated children only. At all centers the patients were under unified management. Analysis of the results obtained at each of the five centers showed no difference of statistical significance between any two of them.

TREATMENT

A detailed account of the treatment will not be given, for this has been reported in papers from all of the five centers: *Whittington*—Rubie and Mohun (2), Calnan, Rubie, and Mohun (3*a* and *b*); *Great Ormond Street*—Cathie and MacFarlane (4); *Oxford*—Smith, Vollum, and Cairns (5); Cairns and Taylor (6), Cairns, Smith, and Vollum (7), Smith and Vollum (8); *Newcastle*—Robertson and Gairdner (9); *Sheffield*—Illingworth and Lorber (10), Lorber (11).

The main treatment at all of the centers consisted of combined intramuscular and intrathecal streptomycin in prolonged courses. In 1947, when experiments were being made with different methods of treatment, intrathecal treatment was not given to all of the patients, but it was given in all cases thereafter. In the large majority of patients, streptomycin alone was used, but the adjuvant properties of some other drugs were also studied, namely, sulphetrone, streptokinase, and intrathecal tuberculin (PPD). Para-aminosalicylic acid (PAS) was used in only a few patients during the four years under review. Generally speaking, the daily intramuscular dose of streptomycin was 2 gm. for adults and 20 mg. per pound of body weight for children, in two divided doses, given for a minimum of four to six months and often for much longer, especially in patients who also had generalized miliary tuberculosis. There was a tendency to give longer courses in the latter years of the period under review. The intrathecal dose of streptomycin

[2] At the end of November, 1949, the Newcastle group was decentralized and, therefore, no patient who was admitted to this center after that date is included.

varied from 25 to 100 mg. daily. In some centers, alternate daily injections were used after the first few weeks, and some allowed "rest periods" between set courses. The main route of administration was lumbar but, in cases of spinal or tentorial blocks, the cisternal and ventricular routes were also used. Occasionally, major neurosurgical procedures were attempted.

RESULTS

The series was analyzed in relation to the age of the patients, stage of the disease on admission, and the type of the disease. The Medical Research Council (12) classifications of the stage and type were adopted.

The results were analyzed according to survival rates at the first and subsequent anniversaries of the patients' admission. This method allows comparison between the results obtained in patients admitted in different years.

Over-all Results

Two-hundred and sixty-six of the 549 patients survived for one year (48.4 per cent). During the second year, 13 patients died, the over-all two-year survival rate being, therefore, 46.1 per cent. The mortality rate during the second year of observation was 4.9 per cent of the survivors at risk at the end of the first year. Of the 466 patients admitted between 1947 and 1949, only one died in the third complete year of observation and, altogether, 212 (45.4 per cent) were alive on the third anniversary of their admission. There were no later deaths in patients admitted in 1947 and 1948, so there was no alteration of the four-year survival rate of those admitted in 1948 and of the four- and five-year survival rates of those admitted in 1947 during *complete* years of observation. There were, however, 5 other late deaths, 3 of them in the third year among patients admitted in 1950 and 2 in the fourth year among patients admitted in 1949. Altogether, therefore, 4 patients died during the third year of observation, 2 in the fourth, and none in the fifth.

As the whole group was observed for two years and as deaths were too rare after that time to affect the survival rates significantly, it appears that further detailed analyses of survival figures can be legitimately restricted to the two-year survival period.

It may be seen from table 1 that there was a striking and statistically significant improvement in the results after the "trial year" of 1947, from a survival rate of 31.6 per cent in 1947 to 49.3 per cent in the remaining years. This difference was not due to any alteration in the composition of the types of patients treated. There was virtually no difference between the results obtained in 1948, 1949, and 1950. As this statement was found to apply to almost all of the results of the subgroups to be presented, it will not be necessary to discuss separately the results for these three years.

Results According to the Stage of the Disease on Admission

In table 2 are shown the results according to the stage of the disease on admission. It may be seen that there was a high degree of correlation between the

stage of the disease on admission and the prognosis. Patients in the early stage fared far better, and nearly 75 per cent of them survived for two years. The difference between 1947 (68.2 per cent) and 1948–1950 (74 per cent) is not statistically significant, indicating that the over-all improvement in the results in the latter years was largely due to the increased survival rates of patients in the intermediate and advanced stages. Only 26.2 per cent of the patients in the inter-

TABLE 1

OVER-ALL RESULTS OF 549 CASES OF TUBERCULOUS MENINGITIS ACCORDING TO LENGTH OF OBSERVATION

YEAR OF ADMISSION	NUMBER ADMITTED	NUMBER SURVIVING AT THE END OF					PERCENTAGE SURVIVING AT THE END OF				
		1 year	2 years	3 years	4 years	5 years	1 year	2 years	3 years	4 years	5 years
1947	101	33	32	32	32	32	32.6	31.6	31.6	31.6	31.6
1948	176	94	89	89	89		53.4	50.5	50.5	50.5	
1949	189	95	92	91			50.2	48.6	48.1		
1950	83	44	40				53.0	48.2			
1947–1950	549	266	253				48.4	46.1			
1947	101	33	32				32.6	31.6			
1948–1950	448	233	221				52.0	49.3			

TABLE 2

THE PROGNOSIS OF TUBERCULOUS MENINGITIS ACCORDING TO STAGE OF DISEASE ON ADMISSION

Follow-up: Two Years

YEAR OF ADMISSION	EARLY			INTERMEDIATE			ADVANCED		
	Number	Alive	Per cent	Number	Alive	Per cent	Number	Alive	Per cent
1947	22	15	68.2	42	11	26.2	25	3	12.0
1948	45	33	73.3	81	42	51.8	41	9	21.9
1949	39	28	71.8	82	47	57.3	57	13	22.8
1950	16	13	81.8	35	17	48.5	27	9	33.3
Total....	122	89	72.9	240	117	48.7	150	34	22.6
1947	22	15	68.2	42	11	26.2	25	3	12.0
1948–1950	100	74	74.0	198	106	54.0	125	31	24.8

mediate stage admitted in 1947 survived for two years, but the survival rate of the 1948–1950 patients was more than double that, namely, 54.0 per cent. Only 12.0 per cent of the 1947 patients in the advanced stage survived, as compared with 24.8 per cent in 1948–1950. All of these differences are significant.

Broadly speaking, therefore, 75 per cent of the patients in the early stage, 50 per cent in the intermediate stage, and 25 per cent in the advanced stage survived with streptomycin treatment. Early diagnosis of all cases would therefore

raise the over-all survival rate to approximately 75 per cent without any improvement in management or the introduction of other drugs.

Thirty-seven patients who developed meningitis while under treatment for miliary tuberculosis were not included in these figures. They will be dealt with in the next section.

Results According to the Type of Disease on Admission

The results according to the type of the disease on admission are shown in table 3. Patients in whom miliary tuberculosis was not demonstrable during life fared better than those who had miliary tuberculosis in addition to the meningitis, irrespective of whether the meningitis and miliary tuberculosis were both present when treatment was started or whether the meningitis developed during treatment of miliary tuberculosis. The difference between the survival rates of those without miliary tuberculosis (49.2 per cent) and those with miliary tuberculosis (40.4 per cent) is significant, but the prognostic influence of the type of disease is not so striking as the stage of disease on admission (figure 1). The improvement in the results from 1947 to 1948–1950 was considerable for both types of disease and is statistically significant. The 1948–1950 results show that more than half of the patients (52.2 per cent) without miliary tuberculosis survived, compared with 44.1 per cent of those with miliary tuberculosis.

TABLE 3

THE PROGNOSIS OF TUBERCULOUS MENINGITIS ACCORDING TO TYPE OF DISEASE

Follow-up: Two Years

YEAR OF ADMISSION	MENINGITIS ONLY			WITH MILIARY TUBERCULOSIS								
				Meningitis on Admission			Miliary → Meningitis			All		
	Number	Alive	Per cent	Number	Alive	Per cent	Number	Alive	Per cent	Number	Alive	Per cent
1947	64	23	35.9	25	6	24.0	12	3		37	9	24.3
1948	117	59	50.4	50	25	50.0	9	5		59	30	50.5
1949	117	65	55.5	61	23	37.7	11	4		72	27	37.6
1950	53	26	49.0	25	13	52.0	5	1		30	14	46.8
Total...	351	173	49.2	161	67	41.6	37	13	35.1	198	80	40.4
1947	64	23	35.9	25	6	24.0	12	3	25.0	37	9	24.3
1948–1950	287	150	52.2	136	61	44.8	25	10	40.0	161	71	44.1

Results According to Age on Admission

The results of treatment in relation to age are presented in table 4. It may be seen that significant improvements in the results were obtained in all age groups from 1947 to 1948–1950 and that the rate of improvement was similar for all three groups. There was no difference between the survival rate of those aged three to fourteen years and those more than fourteen years of age. Subdivision

of the patients in the more than fourteen-year group into two numerically equal halves, that is, into ages fourteen to twenty years and more than twenty years also showed no difference in the survival rates.

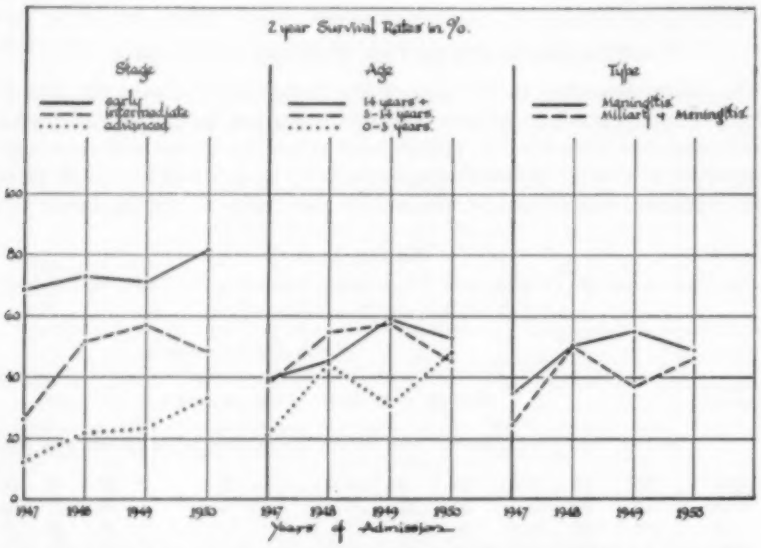

FIG. 1. The two-year survival rates of 549 cases of tuberculous meningitis, according to year of admission, stage of disease, age on admission, and type of disease.

TABLE 4

THE PROGNOSIS OF TUBERCULOUS MENINGITIS ACCORDING TO AGE

Follow-up: Two Years

YEAR OF ADMISSION	0 TO 3 YEARS			3 TO 14 YEARS			14 YEARS AND OVER		
	Number	Alive	Per cent	Number	Alive	Per cent	Number	Alive	Per cent
1947	42	9	21.4	36	14	38.8	23	9	39.1
1948	47	21	44.6	94	52	55.3	35	16	45.7
1949	68	21	30.8	74	43	58.1	47	28	59.5
1950	31	15	48.4	33	15	45.4	19	10	52.6
Total....	188	66	35.1	237	124	52.3	124	63	50.8
1947	42	9	21.4	36	14	38.8	23	9	39.1
1948–1950	146	57	39.0	301	110	54.7	101	54	53.4

The prognosis of those less than three years of age was significantly worse. In 1948–1950, a little less than 40 per cent of the patients survived in the less than three years of age group and more than 50 per cent survived in two groups

of those more than three years of age. The prognostic significance of age, therefore, was not as pronounced as that of the stage of the disease on admission (figure 1). Furthermore, of the 188 patients less than three years of age on admission, 75 (40 per cent) were in an advanced stage of the disease; while, of the 361 patients more than three years of age, only 20 per cent were in that stage. These figures indicate that the greater mortality in children less than three years of age was due largely to the delayed diagnosis in this age group and that, with earlier diagnosis, the prognosis for younger children need not necessarily be worse than in the older age groups.

The Condition of the Survivors

Mere survival figures do not indicate accurately the measure of success obtained in the treatment of tuberculous meningitis. A proportion of the survivors suffered variable degrees of handicap because of sequelae which may be attributed to the disease or to the toxic effects of streptomycin. Such sequelae may either disappear in the course of prolonged observation or they may become apparent only long after the patient's recovery. For these reasons it is important to assess the condition of the survivors after an adequate period of observation.

The 247 survivors of the present series have all been observed for a minimum of two and one-half years, and 207 of them for between three and one-half and six years. Their condition has been reassessed in 1953, and the results are presented below. A recent relapse of the meningitis in 2 of them necessitated retreatment, and those 2 are not included in the analysis. In the case of patients who developed meningitis during treatment for miliary tuberculosis, the stage of the disease, for purposes of analysis, was considered to be that at which treatment for the meningitis was begun. As two-thirds of them were in the early stage of meningitis and as the results in them were not so favorable as in other types of early cases, their inclusion led to some reduction of the over-all survival rate of the early cases.

In table 5 it is shown that, of the 245 survivors, 157 (64 per cent) had no sequelae whatever. Of the early cases, nearly 75 per cent of the survivors were without sequelae, as compared with 60 per cent of the surviving intermediate cases and only 40 per cent of the surviving advanced cases. The incidence of neurologic sequelae was directly related to the stage of the disease at which treatment was begun. Altogether, 27 (11 per cent) of the survivors were left with sequelae of moderate severity (excluding deafness), consisting of either residual hemiparesis, visual defects not amounting to blindness, occasional fits, or moderate degrees of mental and behavior disorders. There was a progressive increase of these sequelae from 5 per cent in the surviving early cases to nearly 20 per cent of the surviving advanced cases. As for severe sequelae, consisting of grave degrees of mental defect, often associated with blindness, deafness, and hemiplegia, severe behavior disorders or of gross neurologic damage, such as complete hemiplegia or a cauda equina syndrome, these were found in 10.5 per cent of all survivors, but in early cases this percentage was only 4 per cent; in intermediate cases, 8.7 per cent; and in advanced cases, 35.5 per cent. The 25 patients in this

category are more properly classified as failures, and many of them live a vegetative existence.

Altogether, 9 early cases (9 per cent of survivors), 26 intermediate cases (22.6 per cent of survivors), and 17 late cases (54.8 per cent of survivors in that group) were complicated by neurologic sequelae, showing that delayed diagnosis, not only prejudiced the possibility of survival, but that the chances of a complete recovery became very remote once the patient reached the advanced stage.

Vestibular damage due to streptomycin was usual but, as compensation for this was practically universal, the survivors have no subjective symptoms. The only remaining disability to consider is deafness. Altogether, 36 patients (14.7 per cent of the survivors) suffered some degree of hearing loss sufficient to be appreciated by the patients as their only residual disability. It is not possible to state the total number who are deaf because several of the survivors with severe

TABLE 5

THE CONDITION OF 245 SURVIVORS*

Follow-up: Two and One-Half to Six Years

STAGE	ALL CASES	NO SEQUELAE		MODERATE DEAFNESS		SEVERE DEAFNESS		MODERATE SEQUELAE		SEVERE SEQUELAE	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Early	99	73	73.7	7	7.0	10	10.0	5	5.0	4	4.0
Intermediate	115	72	62.6	5	4.3	12	10.4	16	13.9	10	8.7
Advanced	31	12	38.7	0	0	2	6.4	6	19.3	11	35.5
Total	245*	157	64.0	12	4.9	24	9.8	27	11.0	25	10.5

* Not including 2 intermediate cases still being treated; including 13 patients who developed meningitis during treatment for miliary tuberculosis and who survived (11 early, 2 intermediate cases).

mental sequelae are of too low intelligence to assess the degree of their hearing. A glance at table 5 shows, however, that there is no correlation between the stage of disease on admission and the incidence of deafness. The incidence of deafness is of the same order in all groups. These figures suggest that streptomycin was the cause of deafness, at least in the large majority of cases. This suggestion was supported by the results of the individual centers. In the two centers in which streptomycin was given for the longest period, both intramuscularly and intrathecally, 19 of 115 survivors became deaf (16.5 per cent), compared with 5 of 130 survivors (3.8 per cent) in the other 3 centers. Two-thirds of the deaf patients were totally deaf; the other third were managing well with hearing aids.

In figure 2 and table 6 are summed up the chances of patients who were admitted to one of the five centers between 1947 and 1950 (inclusive) according to the stage of the illness on admission. The prognosis of the intermediate cases was almost the same as that of the whole series.

It is seen that 66.6 per cent of the patients in the early stage, less than 50

per cent in the intermediate stage, and only 20 per cent in the advanced stage survived. As for the quality of recovery, full recovery without sequelae occurred in 10 per cent of the advanced cases, 30 per cent of the intermediate cases, and

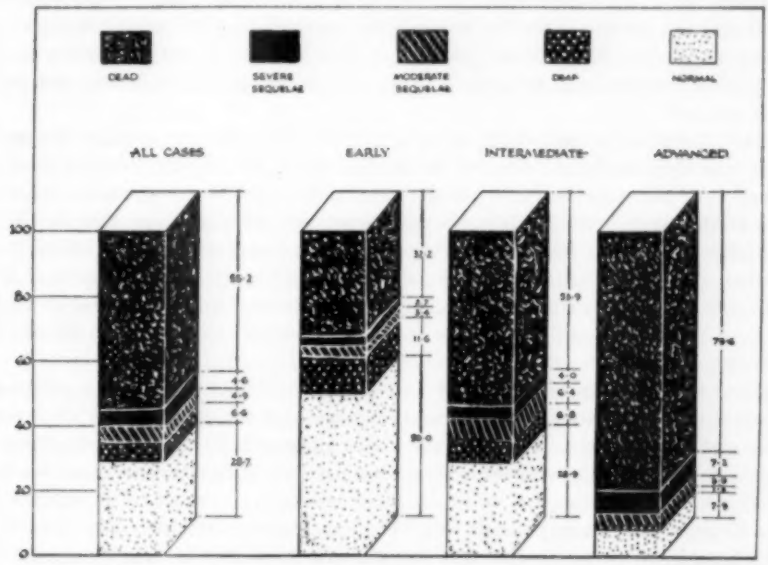

FIG. 2. The fate of 549 cases of tuberculous meningitis, expressed in percentages.

TABLE 6

THE FATE OF 549 PATIENTS ADMITTED WITH TUBERCULOUS MENINGITIS 1947–1950 IN PERCENTAGES

	ALL CASES	STAGE OF DISEASE ON ADMISSION		
		Early	Intermediate	Advanced
Alive	44.8	67.8	44.1	20.4
Normal	28.7	50.0	28.9	7.9
Deaf	6.6	11.6	6.8	1.3
Moderate sequelae	4.9	3.4	6.4	3.9
Severe sequelae	4.6	2.7	4.0	7.2
Dead	55.2	32.2	53.9	79.6

50 per cent of the early cases. Useful recovery (excluding those with severe sequelae) occurred in 65 per cent of the early cases, 42 per cent of the intermediate cases, and 13 per cent of the advanced cases. Patients with early disease, therefore, had a five times better chance of complete or useful recovery than patients with advanced lesions.

Results in 1951

This investigation concluded with patients who were admitted up to the end of 1950. Three of the participating centers (Whittington, Oxford, and Sheffield) remained under the same unified direction during 1951, and their survival figures for that year are available for preliminary comparison. The major change in treatment in 1951 was the routine use of PAS and the more frequent use of intrathecal tuberculin as adjuvants to the streptomycin. Isoniazid was not yet available.

These 3 centers admitted 89 patients in 1951, and the composition of these cases was very similar to those in the earlier years. The survival figures at the end of the first anniversary, however, were better. Fifty-seven patients (64 per cent of the total) survived for one year, compared with 32.6 per cent in 1947 and 52.0 per cent in 1948–1950. This over-all improvement did not affect the survival rate of the advanced cases, which was still only 26 per cent (6 of 23 patients). The survival rate of patients in the intermediate stage rose to 70.7 per cent (29 of 41) and of patients in the early stage to 88 per cent (22 of 25 patients).

These figures indicate that improved methods of treatment and increasing experience have resulted in the survival of 80 per cent of those patients who were conscious on admission. The need for earlier diagnosis is, therefore, again emphasized. These results also show that whatever new drugs may be available in the future for the treatment of tuberculous meningitis, it must be remembered that 80 per cent of those patients who were conscious on admission may be saved with combined intramuscular and intrathecal streptomycin treatment, using PAS as a routine and intrathecal tuberculin as an adjuvant in selected cases.

SUMMARY

The results of streptomycin treatment in 549 consecutive cases of tuberculous meningitis were analyzed. The patients were admitted between 1947 and 1950, inclusive.

The treatment consisted in most cases of prolonged, combined, intramuscular and intrathecal administration of streptomycin.

The over-all two-year survival rate of 101 patients admitted in 1947 was 31.6 per cent and of 448 patients admitted in 1948–1950 was 49.3 per cent. Later deaths were very rare.

The most important prognostic factor was the stage of the disease on admission. Of 100 patients admitted in 1948–1950 in the early stage of the disease, 74 per cent survived; of 198 intermediate cases, 54 per cent survived; and of 125 advanced cases, 24.8 per cent survived.

Patients without demonstrable miliary tuberculosis during life had an 8 per cent better survival rate than those who had miliary tuberculosis in addition to the meningitis. In 1948–1950, 52.2 per cent of 287 patients without miliary tuberculosis survived, and 44.1 per cent of 161 patients who had miliary tuberculosis and meningitis survived.

There was no difference between the survival rates of patients in the age groups three to fourteen years (54.7 per cent of 301 patients in 1948–1950) and more than fourteen years (53.4 per cent of 101 patients in 1948–1950); but the prognosis for those less than three years of age was worse, 39 per cent of 146 patients having survived in 1948–1950. This less favorable prognosis in younger children was partly due to delay in diagnosis. Forty per cent of all patients less than three years of age (188 cases) were in the advanced stage, but only 20 per cent of the remaining 361 patients were in the advanced stage on admission.

The 245 survivors were followed for two and one-half to six years. In all, 64 per cent had no sequelae whatever. Seventy-five per cent of those admitted in the early stage, 60 per cent of those in the intermediate stage, and 40 per cent of those in the advanced stage had no sequelae. The incidence of moderate or severe neurologic sequelae was least among early cases (9 per cent) and greatest among advanced cases (55 per cent). In 14.7 per cent of all survivors, deafness was the only residual damage, and two-thirds of these were totally deaf. It is presumed that this complication was usually a consequence of the streptomycin treatment and was not caused by the meningitis.

The over-all one-year survival figure of 64 per cent for 89 patients who were admitted in 1951 represented a considerable improvement. The survival rate for early cases rose to 88 per cent, for intermediate cases to 70.7 per cent, but remained only 26 per cent for advanced cases. In all, 80 per cent of the 66 patients who were admitted fully conscious survived for one year.

SUMARIO

Los Resultados del Tratamiento de Quinientos Cuarenta y Nueve Casos de Meningitis Tuberculosa

Este análisis comprende el resultado del tratamiento con estreptomicina en 549 casos consecutivos de meningitis tuberculosa, recibidos entre 1947 y 1950, inclusive.

En la mayor parte de los casos, el tratamiento consistió en la administración intramuscular e intratecal prolongada y combinada de estreptomicina.

El coeficiente global de sobrevivencias de dos años para 101 enfermos admitidos en 1947 fué de 31.6 por ciento y para 448 enfermos admitidos en 1948–1950 de 49.3 por ciento. Las muertes tardías fueron rarísimas.

El más importante factor en el pronóstico fué el período de la enfermedad al ingreso del sujeto. De 100 enfermos recibidos en 1948–1950 en el período incipiente de la dolencia, 74 por ciento sobrevivieron; de 198 casos intermedios, 54 por ciento; y de 125 casos avanzados, sobrevivieron 24.8 por ciento.

Los enfermos sin granulia observable en vida tuvieron un coeficiente de sobrevivencia 8 por ciento mejor que los que tenían granulia además de meningitis. En 1948–1950, sobrevivieron 52.2 por ciento de 287 enfermos sin granulia y 44.1 por ciento de 161 que tenian granulia.

No hubo diferencia en los coeficientes de sobrevivencia en los enfermos de los grupos de tres a catorce años de edad (54.7 por ciento de 301 enfermos en 1948–1950) y en los de más de catorce años (53.4 por ciento de 101 enfermos en 1948–1950); pero el pronóstico fué peor para los de menos de tres años de edad, habiendo sobrevivido 39 por ciento de 146 enfermos en 1948–1950. Este pronóstico menos favorable en los niños más pequeños se debió en parte a demora en el diagnóstico. Dos quintas partes de todos los enfermos de menos de tres años (188) se encontraban en el período avanzado, mientras que, a su ingreso, sólo la quinta parte de los otros 361 pacientes se hallaban en dicho período.

Los 245 sobrevivientes fueron mantenidos en observación de dos y medio a seis años. En conjunto, 64 por ciento no manifestaron la menor secuela. Tres cuartas partes de los recibidos en el período incipiente, tres quintas partes de los del período intermedio y dos quintas partes de los del período avanzado no tuvieron secuelas. La incidencia de secuelas neurológicas moderadas o graves alcanzó el mínimo (9 por ciento) en los casos incipientes y el máximo (55 por ciento) en los avanzados. En 14.7 por ciento de todos los sobrevivientes, la sordera fué el único daño residual y dos terceras partes de los sobrevivientes quedaron totalmente sordos. Esta complicación pareció deberse a la estreptomicinoterapia y no a la meningitis misma.

La cifra global de 64 por ciento de sobrevivencias de un año para 89 enfermos admitidos en 1951 representó una notable mejora, elevándose a 88 por ciento para los casos incipientes y a 70.7 por ciento para los intermedios, pero no pasando de 26 por ciento en los avanzados. En conjunto, cuatro quintas partes de los 66 enfermos que, a su ingreso, estaban plenamente conscientes sobrevivieron un año o más.

RESUME

Les résultats du traitement de cinq cent quarante-neuf cas de méningite tuberculeuse

Les résultats de la streptomycinothérapie dans une série de 549 cas de méningite tuberculeuse ont été analysés. Les malades avaient été hospitalisés entre 1947 et 1950, inclusivement.

Dans la plupart des cas le traitement a consisté en administration prolongée de streptomycine par les voies musculaire, intramusculaire et intrarachidienne combinées.

Les taux de survie pour l'ensemble des 101 patients admis en 1947 était 31,6 pour cent, et 49,3 pour cent pour les 448 patients admis en 1948–1950. Les décès plus tardifs étaient très rares.

Le facteur pronostique le plus important est le stade de l'affection lors de l'admission. Sur un nombre de 100 malades admis en 1948–1950 au stade de début de la maladie, 74 pour cent survivaient; sur 198 cas au stade intermédiaire, 54 pour cent survivaient; sur 125 cas avancés 24,8 pour cent survivaient.

Chez les malades indemnes de tuberculose miliaire apparente au cours de la vie, le taux de survie était plus favorable que celui des cas où la tuberculose miliaire s'associait à la méningite. En 1948–1950, 52,2 pour cent des 287 patients indemnes de tuberculose miliaire et 41,1 pour cent des 161 malades affectés de tuberculose miliaire survivaient également.

Il n'y avait aucune différence entre les taux de survie des malades du groupe d'âge 3-14 ans (54,7% sur 301 patients en 1948–1950) et de ceux au-delà de 14 ans (53,4% sur 101 patients en 1948–1950; le pronostic était cependant pire pour les malades au-dessous de 3 ans (sur 146 patients, 39 pour cent ayant survécu en 1948–1950). Ce pronostic moins favorable chez le jeune enfant était partiellement dû au retard du diagnostic. Au moment de l'admission, deux cinquièmes de la totalité des malades au-dessous de trois ans (188 cas) étaient au stade avancé de l'affection, alors qu'un cinquième seulement des 361 patients restants étaient au stade avancé de l'affection.

Les 245 survivants furent suivis pendant deux ans et demi à six ans. Dans l'ensemble, 64 pour cent n'ont présenté aucune séquelle. Trois-quarts des malades hospitalisés au stade de début, trois cinquièmes de ceux au stade intermédiaire et deux cinquièmes au stade avancé ne présentaient pas de séquelles. La fréquence de séquelles neurologiques de caractère modéré ou sévère était la plus réduite parmi les cas au début (9%) et la plus grande parmi les cas avancés (55%). Pour l'ensemble des survivants, la surdité constituait l'unique séquelle chez 14,7 pour cent d'entre eux; la surdité était totale chez deux tiers d'entre eux. Cette complication a été considérée comme attributable à la streptomycinothérapie et non à la méningite en soi.

Le taux d'ensemble de survie d'un an, qui est 64 pour cent pour 89 patients hospitalisés en 1951, représente une amélioration considérable. Le taux de survie pour les cas au début a atteint 88 pour cent; pour les cas au stade intermédiaire, 70,7 per cent; il n'a été que de

26 pour cent pour les cas avancé. En tout, quatre cinquièmes des 66 patients admis à la phase non comateuse ont survécu pendant une année.

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THE UNHOSPITALIZED TUBERCULOUS PATIENT[1]

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INTRODUCTION

The public announcement of the effect of isoniazid on tuberculosis in February, 1952, provided the stimulus for an intensive study of chemotherapy in ambulant patients. Preliminary observations in hospitalized cases had indicated that isoniazid more nearly fulfilled the requirements for this type of investigation than any other agent. It was relatively nontoxic, easy to use, and inexpensive. It produced marked symptomatic improvement, with reduction in cough and expectoration, and gain in weight. Most important, its use resulted in disappearance of tubercle bacilli from the sputum in a substantial proportion of patients in a relatively short time. This made it a particularly desirable preparation for the purpose of the present study, which was aimed at determining the place of chemotherapy for ambulatory patient s in the public health control of tuberculosis.

PLAN OF INVESTIGATION

In March and April, 1952, a group of 110 patients was started on isoniazid therapy. The patients were chosen on the basis of the following criteria: repeated demonstrations of tubercle bacilli in the sputum within the preceding six months; fibrocaseous disease not suitable for collapse or surgical therapy because of extent of disease or complicating factors; and suitable home with cooperative patient and family. No patient was included in whom isoniazid would serve as a substitute for more firmly established forms of treatment. With very few exceptions these criteria have been adhered to rigidly.

The effect of these strict standards is reflected in the composition of the group studied as shown in table 1. Further evidence of the chronicity of the disease in this group is provided by analysis of the length of time the patients had been known to have tuberculosis and their clinical history before isoniazid treatment was started. This is illustrated in table 2.

At the beginning of the study, all patients received a complete clinical examination, including urine analysis and blood count. Patients were re-examined at the therapy centers weekly for the first three months and every two weeks thereafter. Roentgenographic examinations were performed every two weeks and tomographic studies when indicated. At each visit two specimens of sputum were collected. They were concentrated, and equal portions (approximately 0.25 ml.) were inoculated on both Peizer-Schechter agar and Löwenstein-Jensen egg media, as well as smeared on a slide for microscopic examination. Cultures of all patients were tested for susceptibility to both isoniazid and streptomycin initially and

[1] From the Bureaus of Tuberculosis and Laboratories, Department of Health, New York, New York.

to isoniazid at frequent intervals during the course of the study. In addition, the pathogenicity for guinea pigs and mice of cultures containing tubercle bacilli was studied on a number of occasions. The results of these studies are given in the papers of Peizer, Widelock, and Klein (1) and Bloch, Widelock, and Peizer (2).

At the time treatment was first started, little information was available concerning the optimal dosage of isoniazid, and no reports had been published on its use in conjunction with other antituberculous drugs. In these circumstances, the choice of a regimen had to be a conservative one and a dosage of 3 mg. of isoniazid[2] per kg. of body weight was chosen. All patients were maintained on this schedule throughout the study.

TABLE 1

AGE, RACE, SEX DISTRIBUTION OF PATIENTS RECEIVING ISONIAZID THERAPY

AGE GROUP	MALE		FEMALE		TOTAL	
	White	Nonwhite	White	Nonwhite	White	Nonwhite
25 to 44	8	7	4	10	12	17
45 to 64	33	14	11	3	44	17
Over 65	17	2	1	0	18	2
Total	58	23	16	13	74	36

TABLE 2

CLINICAL HISTORY PRIOR TO ISONIAZID THERAPY

108 Patients

	NUMBER	PER CENT
Duration of disease		
Less than 1 year	8	7.4
1 to 5 years	50	46.3
5 to 10 years	28	25.9
Over 10 years	22	20.4
Previous hospitalization	89	82.4
Previous collapse or surgical treatment	25	23.1
Previous chemotherapy	50	46.3

During the entire period in which antimicrobial therapy was being given, the patient was advised to observe the same routine of physical activity as previously. For most, this meant full-time employment, performing routine household duties, or doing odd jobs. Approximately 40 per cent were receiving public assistance and, therefore, were technically unemployed. The public health nurses who visited the homes of the patients reported that advice with respect to activity was being followed closely.

OBSERVATIONS

Twenty-two of the 110 patients originally included failed to complete the full course of treatment of approximately eight months. In 12 of the 22, treat-

[2] Supplied by Nepera Chemical Co., Inc. as Pyricidin.

ment was terminated during the first three months, in 5 more in the second three months, and in the remainder at subsequent periods. The reasons for the discontinuance of therapy in these 22 patients are given in table 3.

TABLE 3

REASONS FOR TERMINATION OF ISONIAZID THERAPY

22 Patients

Death of patient	3
Tuberculosis	1
Other than tuberculosis	2
Hospitalization	8
Tuberculosis	6
Other than tuberculosis	2
Toxic reaction	5
Skin rash	2
Urinary retention	2
Exacerbation of asthma	1
Discontinued by patient	5
Other reason	1

TABLE 4

CHANGE IN WEIGHT AND VOLUME OF SPUTUM AFTER 6 MONTHS OF ISONIAZID THERAPY

93 Patients

	WEIGHT		SPUTUM	
	Number	Per Cent	Number	Per Cent
Increase	72	77.4	5	5.4
Less than 5 pounds	26			
5 to 10 pounds	36			
Over 10 pounds	10			
Decrease	14	15.0	49	52.7
No change	7	7.5	39	41.9

Clinical and Roentgenographic Results

An evaluation of the clinical status of the 93 patients who had completed six months of treatment was made at the end of that period and is shown in table 4. None of the patients had any significant degree of fever. The maximum effect of the drug was observed during the first three months of its application, with a general tendency for the same pattern of response to persist at a lower level thereafter.

Roentgenographic studies: Serial roentgenograms of the 88 patients who completed the full course of isoniazid therapy were reviewed and the cases were classified as showing moderate or marked improvement, slight improvement, no change, or worsening. In each instance the classification was based on com-

parison of the roentgenographic findings at the beginning and end of the period of treatment, interval changes being disregarded.

Clearing of infiltrative lesions or reduction in the size of cavities was considered as evidence of improvement, extension of the disease or enlargement of cavities as worsening.

The changes noted on the roentgenograms at the end of eight months of treatment are indicated in table 5. The conventional postero-anterior films showed apparent cavity closure in 5 patients, which has been confirmed by tomographic examination in 3 patients.

The response to therapy was generally more favorable in those patients whose disease was of less than five years' duration and largely exudative in character. Most of these patients were young Negro females. Surprisingly, marked improvement in the roentgenograms of several men in their sixties was also seen.

TABLE 5

ROENTGENOGRAPHIC STATUS AFTER 8 MONTHS OF ISONIAZID THERAPY

88 Patients

	NUMBER	PER CENT
Improvement	41	46.6
Moderate or marked	14	
Slight	27	
No change	36	40.9
Worse	11	12.5

Bacteriologic Studies

Two methods of analysis were used in the appraisal of the bacteriologic status of patients who received chemotherapy: the customary approach of determining the frequency of the finding of tubercle bacilli on smear and culture; and semiquantitative evaluation of the number of colonies produced by the tubercle bacilli in the sputum at each examination, with notation of the quantitative variation during different periods of this study.

For the purpose of the first method of analysis, the eight-month period of the study was divided into two-month intervals, and the status at the beginning and at the end of treatment were compared. The patients were divided into four groups. Those classified as predominantly "positive" had positive examinations for tubercle bacilli on more than 50 per cent of examinations; those designated frequently "positive" had 20 to 50 per cent positive examinations; and those classified as rarely "positive" yielded tubercle bacilli in less than 20 per cent of all examinations. Patients whose specimens failed to show tubercle bacilli were classified as consistently "negative."

The findings on smear and culture examinations were analyzed separately and are presented in table 6. Fifteen patients had consistently "negative" cultures at the end of treatment, a "conversion" rate by culture of 17.6 per cent. All but 2 of these 15 had been predominantly or frequently positive for tubercle

bacilli on culture at the beginning of treatment. The 29 patients in whom tubercle bacilli could not be found on examination of any concentrated specimen during the last two-month treatment period represented an over-all "conversion" rate by smear of more than 31 per cent. More than 75 per cent of these patients had been predominantly or frequently positive for tubercle bacilli at the onset of therapy.

In the second method of analysis, the growth on each culture was evaluated as 4 plus, 3 plus, 2 plus, 1 plus, less than 1 plus, and negative, according to the number of colonies of *M. tuberculosis* produced. The exact technique, as well as the statistical justification for its reliability and consistency, will be published

TABLE 6

CHANGE IN FREQUENCY OF POSITIVE BACTERIOLOGIC FINDINGS ON SMEAR AND CULTURE
88 Patients

	SMEAR		CULTURE	
	First 2 Months	Last 2 Months	First 2 Months	Last 2 Months
Predominantly positive	54	41	75	65
Frequently positive	24	10	9	5
Rarely positive	8	8	3	2
Consistently negative	2	29	1	16

TABLE 7

CHANGE IN ROENTGENOGRAPHIC STATUS OF 19 PATIENTS WITH DECREASE IN COLONY COUNT BY THIRTY-SECOND WEEK

ROENTGENOGRAPHIC STATUS	NUMBER	PER CENT
Worse	0	0.0
No change*	4(1)*	21.1(5.2)*
Improvement	15	78.9

* Figures if cases without cavitation are excluded.

in the near future. With this method of analysis, the following results were obtained, as illustrated in tables 7, 8, and 9.

A relationship between roentgenographic worsening and high colony counts seemed to exist as all patients with roentgenographic worsening had colony counts less than 1 plus. There was also a suggestion that roentgenographic improvement was directly correlated with cultures decreasing from 1 plus to less than 1 plus, as shown in table 7. A similar relationship seemed to be present between changes in the roentgenograms and the frequency of positive bacteriologic findings.

Relation of over-all results to previous antimicrobial therapy: An attempt was made to relate the behavior of the patient to the history of previous antimicrobial therapy. There was suggestive evidence that patients who had received such treatment did less well than those who had not. The numbers involved were too small and the histories were too incomplete to permit drawing definite conclusions.

Drug resistance: The development of drug resistance was studied in the laboratory during the entire thirty-two-week period of treatment with isoniazid. Equal quantities of the concentrates of all sputum specimens were spread on the culture media containing varying amounts of the drug, as well as upon control media. The development of resistant colonies was noted. The exact details of the technique, as well as the complete details of the results, will be given in a future publication. In tables 8 and 9 are summarized the more pertinent data

TABLE 8

DEVELOPMENT OF RESISTANCE AT 3 AND 8 MONTHS

87 Patients

RESISTANCE γ per ml.	3 MONTHS		8 MONTHS	
	Number	Per Cent of Patients With Resistant Organisms	Number	Per Cent of Patients with Resistant Organisms
None	21	—	22	—
0.1	19	28.8	3	4.6
0.5	4	6.1	5	7.7
1.0	13	19.7	10	15.4
5.0	30	45.4	47	72.3

TABLE 9

RELATIONSHIP BETWEEN RESISTANCE AND COLONY COUNT AT 8 MONTHS

87 Patients

RESISTANCE γ per ml.	COLONY COUNT						
	Negative	< 1+	1+	2+	3+	4+	Total
None	18	3	1	0	0	0	22
0.1	1	2	0	0	0	0	3
0.5	0	1	1	2	1	0	5
1.0	0	2	1	3	3	1	10
5.0	0	3	8	9	15	12	47
Total	19	11	11	14	19	13	87

with respect to the patients who completed the entire eight months of treatment with isoniazid.

None of the strains of tubercle bacilli was resistant to 0.1 γ of isoniazid per ml. prior to contact with the drug. At the end of the first three months, resistance to 0.1 γ accounted for 19 of the 66, or 28.8 per cent, of the resistant specimens. By the eighth month this was reduced to 4.6 per cent, the difference being accounted for by an increase in the number of strains resistant to 5.0 γ, as indicated in table 8.

The subsequent behavior of the tubercle bacilli resistant to 0.1 γ of isoniazid

per ml., as well as the other strains, is more clearly demonstrated in table 9. In this table, the relationship between the resistance developed and the colony counts at the eighth month can be observed. It is interesting to note that conversion to a negative culture occurred only when the tubercle bacilli were never resistant to more than 0.1 γ of isoniazid. Furthermore, the bulk of the cultures evaluated at 1 plus or higher were resistant to at least 0.5 γ. A similar correlation between frequency of cultures positive for tubercle bacilli and the presence of resistant strains was also noted.

In view of the above, the following tentative bacteriologic conclusions are offered:

The concentrations of isoniazid for drug-susceptibility testing should be 0.1 γ, 1.0 γ, and 5.0 γ per ml. of culture medium.

Resistance to a maximum of 0.1 γ should be considered only as a *warning* to the clinician that greater resistance may soon develop.

If resistance to 1.0 γ or to 5.0 γ is present, it is probable that the colony count will remain at 1 plus or higher.

When worsening is noted on the roentgenogram at the eighth month, resistance to 1.0 γ or more is probably also present.

DISCUSSION

In discussing the treatment of "the unhospitalized tuberculous patient," consideration must be given to the wide variety of cases included in this category. The acutely ill patient awaiting admission to a hospital, the patient recently discharged after surgical intervention, and the so-called "good chronic" are all unhospitalized cases of tuberculosis. Although each may be receiving antimicrobial therapy, they differ in many important respects.

A sharp distinction must be drawn between the application of chemotherapy as part of a home-care program, which is merely an extension of the hospital, and its employment as an alternative to institutionalization in the form of ambulatory treatment. The patient awaiting admission, carried on pre-hospital home care, will usually receive as close an approximation to an institutional regimen as possible, including maximal rest and medication administered in the home. The patient recently discharged from the hospital who is part of a post-hospital home-care program will generally be placed on a schedule of limited physical activity. In both instances, the drug therapy received at home will represent only a small part of the over-all treatment of the patient's tuberculosis. On the other hand, no attempt is made to change the normal routine or restrict the activity of the patient on true ambulatory treatment. In such cases, chemotherapy represents the decisive element in the management of the patient's tuberculosis and can be so evaluated.

The limitations of the present study were clearly recognized from the very outset. Of 9,000 unhospitalized patients with tuberculosis in New York City, only 110 were selected to receive isoniazid therapy, far too small a sample to warrant drawing statistically valid conclusions. Furthermore, the group investigated was in no sense representative of the entire unhospitalized tuberculosis population of the city. The guiding principle in selection was not to include

patients for whom isoniazid would serve as a substitute for more firmly established forms of treatment. This confined the material almost exclusively to ambulatory patients not suitable for surgical or collapse therapy because of age, extent of disease, or complicating factors.

Another limiting factor in the study was the type of chemotherapeutic regimen employed. Great caution in the avoidance of toxic effects, particularly in elderly patients, was considered essential. The dosage schedule of 3 mg. of isoniazid per kg. of body weight was minimal and, in the light of present standards, might be considered inadequate. Moreover, isoniazid alone was used throughout the study and there was no opportunity to take advantage of combinations of drugs which have since proved more effective in terms of clinical response and delay of the emergence of resistance.

In these circumstances, it is believed fair to conclude that the results are close to the minimum that can be expected from antimicrobial therapy in unhospitalized patients. The sputum conversion rate of almost 18 per cent on repeated culture and more than 30 per cent on smears of concentrates is a substantial accomplishment in the type of completely ambulant patients of the present study.

What may well be the most significant feature of the present study was the change in the behavior and attitude of the patients who received treatment. The records of many of them indicated a long-standing lack of cooperation in both medical supervision and observation of precautions against the spread of their disease. Clinic appointments had been kept irregularly or not at all. During the eight consecutive months of treatment, this same group traveled long distances in all kinds of weather to make weekly or biweekly clinic visits. Their habits at home showed similar improvement. This cooperative attitude remained even after their first enthusiasm for the "wonder drug" had worn off. A more striking testimonial to the change in the chronic disease patient when the pessimism of good advice is replaced by the optimism of treatment would be hard to find.

These observations are of particular importance in relation to the general problem of the treatment of the unhospitalized patient with tuberculosis. Until recently there was little public recognition of the fact that such a problem existed. The opinion was widely held that an institution was the only place to treat every active case of tuberculosis, despite the evidence provided by mass surveys that thousands of persons had healed their disease spontaneously and the demonstration that antimicrobial treatment could be successfully given in the homes of private patients. This point of view had become even less realistic in the face of continued bed shortages resulting from the increased length of hospital stay and larger proportion of "good chronics" accompanying more extensive and prolonged use of antimicrobial therapy.

Fortunately, a more logical approach to the subject of the treatment of the unhospitalized tuberculous patient is now emerging. What is needed at this time is not hospital or home treatment but a plan for the coordinated management of each patient, utilizing all of the available facilities to the maximum. Such a program will call for the application of the most effective therapeutic regimens, given in the home when feasible; in the hospital, when not. It will demand the

close correlation of medical care in the home with surgical care in the hospital. And it will require compromise in the allocation of institutional beds between the concern of the clinician with the complete cure of the individual patient and of the health officer with the complete protection of the community. The experience with isoniazid in ambulatory patients, as reported here, should be regarded as but one step in this direction, part of the framework of a coordinated all-out attack on tuberculosis.

SUMMARY

A group of 110 ambulatory patients with chronic tuberculosis were treated with isoniazid in dosage of 3 mg. per kg. of body weight daily. Eighty-eight completed eight months of treatment.

No significant toxic reactions were observed.

Gain in weight and reduction in the volume of sputum were noted in a substantial proportion of all patients.

Some degree of roentgenographic improvement was noted in 47 per cent of those patients who completed eight months of treatment, and in 16 per cent there was moderate to marked improvement. Roentgenographic worsening occurred in 11 per cent of the group.

Reduction in the frequency of positive bacteriologic findings and in the number of colonies of tubercle bacilli isolated was observed in most instances. Complete sputum "conversion" by culture was observed in 18 per cent of patients. In 31 per cent of cases, organisms could not be found in smears of concentrated sputum specimens.

Improvement in bacteriologic status was associated with failure to develop resistance to more than 0.1 γ of isoniazid.

When roentgenographic worsening was noted, cultures almost invariably showed large numbers of colonies of tubercle bacilli and the strains were resistant to 1.0 γ or more of isoniazid.

This study indicates that the treatment of ambulatory patients with isoniazid, when properly integrated with all other available therapeutic measures, has a definite place in the public health control of tuberculosis.

SUMARIO

El Tuberculoso sin Hospitalizar

Un grupo de 110 enfermos ambulantes con tuberculosis crónica fué tratado con isoniacida a dosis de 3 mg. por kg. de peso diariamente. Ochenta y ocho completaron ocho meses de tratamiento.

No se observaron reacciones tóxicas de importancia.

En una proporción substancial de los enfermos notáronse aumento de peso y disminución del volumen de esputo.

Observóse alguna mejoría radiográfica en 47 por ciento de los enfermos que cumplieron ocho meses de tratamiento; y en 16 por ciento, hubo mejoría que varió de moderada a notable. En 11 por ciento, hubo empeoramiento.

Descubrióse reducción de la frecuencia de los hallazgos bacteriológicos positivos y del número de bacilos presentes, con viraje completo del esputo en 31 por ciento de los enfermos en los frotes y en 18 por ciento en los cultivos.

El mejoramiento del estado bacteriológico se asoció con falta de formación de resistencia a más de 0.1 γ de isoniacida.

Cuando se notó empeoramiento en las radiografías, los cultivos fueron casi siempre altamente positivos y había resistencia a 1.0 γ o más de isoniacida.

Este estudio indica que el tratamiento de los tuberculosos ambulantes con isoniacida tiene su puesto bien definido en la lucha sanitaria contra la tuberculosis.

RESUME

Le tuberculeux non hospitalisé

Un groupe de 110 malades ambulants affectés de tuberculose chronique a été traité par l'isoniazide à la dose quotidienne de 3 mg. par kg. de poids. On a administré la durée du traitement a été de huit mois chez 88 d'entre eux.

Aucune réaction appréciable d'intolérance n'a été observée.

Le gain de poids et la réduction de volume des crachats ont été observés dans une proportion importante du groupe.

Un certain degré d'amélioration des radiogrammes a été observé chez 47% des malades ayant reçu le traitement de huit mois et, chez 16% d'entre eux, le degré d'amélioration variait entre modéré et marqué. L'aggravation s'est produite chez 11% des malades.

Une réduction de la fréquence des résultats bactériologiques positifs et du nombre de bacilles présents a été observée; une conversion complète s'est manifestée chez 31% des malades en ce qui concerne l'étalement, et 18% en ce qui concerne la culture.

L'amélioration de l'état bactériologique coïncidait avec l'absence de résistance à une dose d'isoniazide supérieure à 0,1 γ.

Quand le radiogramme montrait une aggravation, les cultures étaient presque invariablement très positives et la résistance à 1 γ, ou plus, d'isoniazide était présente.

Cette étude indique que le traitement par l'isoniazide des malades ambulants a une place définie dans le contrôle de la tuberculose par les services de Santé publique.

Addendum

Follow-up observations eight to twelve months after start of ambulatory treatment program: At the end of eight months of treatment with isoniazid, those patients who showed definite roentgenographic or bacteriologic improvement, or who had sputum containing bacilli still sensitive to 0.1 γ of isoniazid, were continued on the same treatment regimen for an additional four months. Those who did not show improvement, who had sputum with bacilli resistant to 0.1 γ of isoniazid but susceptible to 100 γ of streptomycin, were placed on 1 gm. of streptomycin twice a week and 12 gm. of PAS daily for the additional period of four months. The remaining patients had all antimicrobial treatment discontinued for the final four-month period.

The results one year after start of ambulatory treatment in 88 patients are shown below:

TREATMENT REGIMEN	TOTAL	ROENTGENOGRAPHIC STATUS			BACTERIOLOGIC STATUS	
		Moderate or Marked Improvement	Slight Improvement or No Change	Deterioration	Conversion* on Microscopic Examination	Conversion* on Culture
Isoniazid: 8 to 12 months	63	12	39	12	31	21
Isoniazid: 8 months; streptomycin-PAS: 4 months	25	5	18	2	15	5
Total	88	17	57	14	46	26
Per cent	100	20	64	16	52	29

* Based on last three consecutive monthly concentrated sputum specimens.

During the final four months of observation, there were 2 additional deaths, one due to a perforated ulcer and the other due to progressive pulmonary tuberculosis.

Acknowledgment

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THE AFTER-HISTORY OF PULMONARY TUBERCULOSIS[1]

I. Methods of Evaluation

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INTRODUCTION

The physician who treats tuberculous patients is vitally concerned with both the clinical course of pulmonary tuberculosis and its ultimate outcome. A reliable means of studying this course and outcome is afforded by the follow-up observations on suitably selected groups of patients. Regarding such groups, several pertinent questions may be proposed, among the more important being: *At any stated number of years after diagnosis, what per cent of the group have arrested disease, what per cent have active disease, and what per cent are dead?* Applied to the individual patient, this question may be rephrased as follows: At any stated number of years after diagnosis, what are his chances of having arrested disease, having active disease, or being dead?

If a physician is favored with a large number of patients who are simultaneously diagnosed and carefully followed for a long time, he will be able to answer directly the proposed questions. More often the physician must content himself with following a modest number of patients whose diagnoses are scattered over a period of years. Hence, at such time as the accumulated data are summarized, the length of follow-up will vary from patient to patient. Information collected and summarized under such conditions has been subjected to a number of methods of analysis, several of which will be noted briefly.

Review of Methods of Analysis

Stadler (1) described the survival of 670 patients who were diagnosed as having pulmonary tuberculosis during the period from April 1, 1893, to April 1, 1901, and who were followed until April 1, 1902. He constructed a table (table 1) showing the per cent of survivors at various intervals after diagnosis. All of the 670 patients in his study were followed at least one year, so that the percentage of survivors one year after diagnosis can easily be computed (638/670 = 95.2 per cent). Of the original 670, 129 were diagnosed during the period between April 1, 1900, and April 1, 1901, and therefore could be followed for only one complete year. The remaining 670 − 129 = 541 patients were diagnosed prior to April 1, 1900, and, hence, were followed at least two years. Of these, 442/541 = 81.7 per cent were alive two years after diagnosis. The percentage of survivors for each succeeding year of follow-up is calculated in a like manner.

More recently this method has been used by Stephens (2) in an excellent study of the after-history of pulmonary tuberculosis. In her appraisal she tabulates the follow-up data three, five, and ten years after diagnosis. At each of these

[1] From Hermann M. Biggs Memorial Hospital, Ithaca, New York.

years the percentage of survivors is divided according to status (able to work, still "curing", "curing" again) and the percentage of dead according to the cause of death (tuberculous, nontuberculous). Berkson and Gage (3) have named the form of analysis used by Stadler and Stephens the "*ad hoc*" method. This method affords useful conclusions when it is assumed that patients with a short follow-up will later have the same experience as is observed in patients with longer follow-up. The percentage of survivors at a stated number of years after diagnosis is an estimate of the probability of the individual patient surviving an equal number of years.

It has long been commonplace in actuarial practice to calculate the probability of surviving a given number of years after a specified age. For example, the probability of surviving seven years after having attained the age of twenty-two is computed by multiplying together the probabilities of living through the twenty-second year of age and through each year thereafter up to and including the twenty-eighth year. This actuarial principle may be applied to the analysis

TABLE 1

SURVIVAL OF 670 TUBERCULOUS PATIENTS ADMITTED TO THE MARBURG POLYCLINIC BETWEEN 1893 AND 1901 (1)

	LENGTH OF FOLLOW-UP IN YEARS								
	1	2	3	4	5	6	7	8	9
Number of patients followed	670	541	477	448	397	357	311	277	243
Number of patients alive after given number of years of follow-up	638	442	347	300	237	193	137	98	62
Per cent of patients alive after given number of years of follow-up	95.2	81.7	72.8	67.0	59.7	54.1	44.2	35.3	25.5

of follow-up data as follows: The probability of surviving, say, ten years after diagnosis is computed by multiplying the probabilities of living through the first year after diagnosis and through each year thereafter up to and including the tenth year.

The first application of this actuarial principle to the follow-up of tuberculosis was made in 1908 by Brown and Pope (4). Hill (5) gives a somewhat fuller explanation of the technique. For each year after diagnosis (or some other definable event), the proportion of survivors is calculated by dividing the number at the end of the year by the number at the beginning of the year. Since each of these proportions is an estimate of the probability of a patient's surviving throughout a specified year, the product of a number of consecutive proportions is an estimate of the probability of surviving an equal number of consecutive years. In computing the latter probability, the tacit assumption is made that patients with a short follow-up will later have the same experience as is observed in those with a longer follow-up.

On the date chosen for summarizing the accumulated follow-up information, the chances are that any given patient will be a certain number of years *plus*

some months away from diagnosis. Some authors (Thompson (6) and Tattersall (7)) discard information pertaining to these "left-over" months (which on the average will be six in number). On the other hand, others (Puffer and associates (8) and Berkson and Gage (3)) make use of the data pertaining to these months by assuming that the patient is, for all practical purposes, under study for a half year (the "half-rule"). Opinions vary whether the use of the half-rule materially improves the estimates of the probabilities (9, 10).

To summarize, in the *ad hoc* method, the percentage of survivors at a stated interval after admission to study is computed first and then used to estimate the probability of a patient's surviving an equal length of time. In the actuarial method, the order of these steps is reversed: First, the probability of a patient's surviving a stated interval is calculated and then used to estimate the percentage of survivors at the end of the interval. The two methods differ in a more important respect, however, than the order in which the described steps are taken. In the *ad hoc* method the probability of surviving, say, ten years after diagnosis is calculated from data concerning only those patients who have at least ten years of follow-up. On the other hand, in the actuarial method the same probability is calculated from data on all the patients under study, irrespective of the length of follow-up. It is clear that the application of the actuarial principle makes much fuller use of the available information than the *ad hoc* method and, hence, leads to more accurate estimates of the probabilities. Since equivalent assumptions are made in the two methods, the actuarial approach appears preferable.

DESCRIPTION OF METHOD

A method is now proposed which employs a principle similar to the actuarial in computing the percentage of survivors for each year of after-history and which in addition subdivides the survivors according to status. Reasonably full use is made of the available data, and a complete answer is provided to the questions stated in the opening paragraph. Furthermore, the method facilitates the study of chronic disease by taking full account of both the duration and recurrence of relapses.

The technique of the proposed method is discussed below. The corresponding procedure using life-table analysis will first be summarized briefly:

1. The number of survivors (L_x) at the end of each year is calculated without the use of the half-rule (since, for reasons given below, all follow-up information pertaining to the "left-over" months is discarded).
2. The number of survivors is subdivided by status according to the observed percentages of active and arrested patients.

The life-table analysis of the present problem will be found in special reference table 1 at the conclusion of this article. It is of interest that Gauld and his coworkers (11) probably made such an analysis but failed to publish the details of the method employed.

To those less familiar with life tables, the technique of calculation described

TABLE 2

PATIENTS TREATED BY THORACOPLASTY 1938–1947 CLASSIFIED BY STATUS AT EACH ANNIVERSARY

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
	LIVING AT ANNIVERSARY		SINCE PREVIOUS ANNIVERSARY					FACTORS		EXPECTED PERCENTAGES				
ANNIVERSARY	Arrested	Active	Died of Tuberculosis	Died of Non-tuberculous Disease	Lost	TOTAL	INCOMPLETE	Provisional	Correction	Arrested	Active	Died of tuberculosis	Died of Non-tuberculous Disease	Lost
0	5	200	—	—	—	205	—	1.0000	0.4878	2.44	97.56	—	—	—
1	100	96	9	—	—	205	—	1.0000	0.4878	48.78	46.83	4.39	—	—
												4.39		
2	140	51	4	—	1	196	—	1.0000	0.4878	68.29	24.88	1.95	—	0.49
												6.34		*0.49*
3	150	36	4	1	—	191	—	1.0000	0.4878	73.17	17.56	1.95	0.49	
												8.29	*0.49*	*0.49*
4	125	30	3	1	2	161	25	1.1553	0.5636	70.45	16.91	1.69	0.56	1.13
												9.98	*1.05*	*1.62*
5	121	25	2	1	—	149	6	1.0403	0.5863	70.94	14.66	1.17	0.59	
												11.15	*1.64*	*1.62*
6	117	20	3	1	1	142	4	1.0282	0.6028	70.53	12.06	1.81	0.60	0.60
												12.96	*2.24*	*2.22*
7	110	16	1	—	—	127	10	1.0787	0.6502	71.52	10.40	0.65		
												13.61	*2.24*	*2.22*
8	93	12	4	1	—	110	16	1.1455	0.7448	69.27	8.94	2.98	0.74	
												16.59	*2.98*	*2.22*
9	69	8	2	—	—	79	26	1.3291	0.9899	68.30	7.92	1.98		
												18.57	*2.98*	*2.22*
10	53	5	—	—	—	58	19	1.3276	1.3142	69.65	6.57			
												18.57	*2.98*	*2.22*

(*1*) Number of years after thoracoplasty.

(*2*) Number of living patients with arrested disease at anniversary.

(*3*) Number of living patients with active disease at anniversary.

(*4*) Number who died of tuberculosis since previous anniversary.

(*5*) Number who died of causes other than tuberculosis since previous anniversary.

(*6*) Number lost since previous anniversary.

(*7*) Total number at anniversary, sum of columns (*2*) to (*6*), inclusive.

(*8*) Number of "incomplete" patients at anniversary. These patients were alive and traced at the previous anniversary but had too short a follow-up to attain the specified anniversary.

(*9*) Provisional factor for anniversary $= \dfrac{\text{column (7)} + \text{column (8)}}{\text{column (7)}}$.

(*10*) Correction factor for anniversary = column (*9*) × correction factor for previous anniversary. The correction factor for anniversary 0 is 100/205 = 0.4878.

(*11*) Expected percentage of living patients with arrested disease at anniversary: column (*2*) × column (*10*).

(*12*) Expected percentage of patients with active disease at anniversary: column (*3*) × column (*10*).

(*13*) Expected percentage of patients dead of tuberculosis at anniversary: column (*4*) × column (*10*). Cumulative percentages in italics.

(*14*) Expected percentage of patients dead of causes other than tuberculosis at anniversary: column (*5*) × column (*10*). Cumulative percentages in italics.

(*15*) Expected percentage of patients lost at anniversary: column (*6*) × column (*10*). Cumulative percentages in italics.

below may be found useful. The numerical results obtained by employing the life-table method are identical to those obtained by using the appropriate anniversary method (see special reference table 2 at the conclusion of this article).

The essential feature of the method is the tabulation of each patient's condition on admission to study and thereafter at yearly intervals (anniversaries). At such anniversaries, a patient can be assigned a clinical status in accordance with the National Tuberculosis Association standards. In contrast to the ease with which these assignments are made, the precise dating of "arrest of disease" and "reactivation of disease" is extremely difficult. Indeed, Sartwell has remarked, "It would not be possible to make 'arrest of disease' (an) end point . . . because this event cannot be sufficiently well oriented in time" (12). The anniversary method avoids such precise dating by ensuring that no patient will be assigned a clinical status more frequently than once a year. Consequently, information pertaining to the "left-over" months is discarded and the half-rule is eliminated.

Use of Anniversary Method in Study of Post-Thoracoplasty Patients

For illustration, data will be used from a ten-year follow-up study of thoracoplasty (13). Two hundred and five patients underwent operation during the years 1937 through 1947 and were followed until January 1, 1951. At the time of operation and at annual intervals (anniversaries) thereafter, each patient was assigned to one of the following categories on the basis of information obtained from the medical record. If the condition of a patient changed between two anniversaries, his new status was recorded at the latter anniversary. For the reasons given above, all information pertaining to the "left-over" months was discarded. For example, if a patient died or became untraced *after* his 1950 anniversary, no account was taken of this fact.

Categories:

Arrested—For six months or more prior to the anniversary, the patient's sputum has been free of tubercle bacilli and his serial chest roentgenograms have been compatible with stable disease.

Active—Within six months prior to the anniversary, the patient's sputum may have contained tubercle bacilli but, if not, serial chest roentgenograms have shown unstable disease. A patient may be assigned to the active or arrested categories a number of times, depending on his postoperative survival and traceability as well as on the length of his follow-up. On the other hand, the assignment of a patient to one of the categories listed below terminates his series of assignments.

Died of tuberculosis—During the year prior to the anniversary, the patient died of progressive tuberculosis. Deaths from any cause occurring within sixty days of thoracoplasty (postoperative deaths) are included arbitrarily in this category at the first anniversary.

Died of nontuberculous causes—During the year prior to the anniversary, the patient died of causes known to be other than tuberculosis.

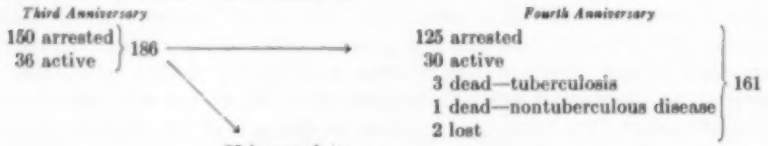
Lost—The patient became permanently lost to follow-up during the year prior to the anniversary.

Incomplete—The patient is alive and traced at that anniversary which occurs in 1950, but he underwent operation too recently to have completed ten years of follow-up. Accordingly, he is assigned either to the "active" or the "arrested" category at the 1950 anniversary and to the "incomplete" category at his next succeeding anniversary.

Columns (*2*) to (*6*) and (*8*) of table 2 show the number of patients assigned to each category at the completion of operation and at ten succeeding anniversaries. There is no difficulty in handling the data collected at the time of operation and at the first three anniversaries since no patients are assigned to the "incomplete" category during this interval. The collection of follow-up information is regarded as completed.

Beginning at the fourth anniversary, patients are assigned to the "incomplete" category. The method of handling them is now illustrated.

There are 186 patients living and traced at the third anniversary and, of these, 25 underwent operation too recently to attain their fourth anniversary. The data collected at the fourth anniversary will pertain to only 186 − 25 = 161 patients, who can be accounted for as follows:

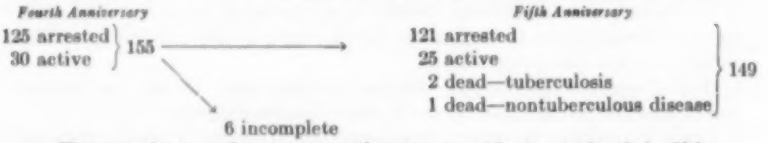


(These patients underwent operation too recently to attain their fourth anniversary)

It is assumed that the 25 "incomplete" patients are a random sample of the 161 other patients and therefore will have the same follow-up experience as is actually observed for the 161 at the fourth anniversary. On this assumption, the number of patients listed in each category under *Fourth Anniversary* will be multiplied by a provisional factor (186/161 = 1.1553) to obtain the number expected in that category if all 186 patients had been followed to the fourth anniversary.

Arrested	125 × 1.1553 = 144.4
Active	30 × 1.1553 = 34.7
Deaths from tuberculosis	3 × 1.1553 = 3.5
Deaths from other causes	1 × 1.1553 = 1.2
Lost	2 × 1.1553 = 2.3

Of the 155 patients living and traced at the fourth anniversary (161 minus 4 deaths and 2 losses), 6 underwent operation too recently to attain their fifth anniversary, leaving 155 − 6 = 149 who can be accounted for as follows:



(These patients underwent operation too recently to attain their fifth anniversary)

Using the same assumption and technique as described above, the numbers listed under *Fifth Anniversary* are multiplied by a provisional factor (155/149 = 1.0403) to obtain the results expected if all of the 155 patients had been followed from the fourth to the fifth anniversary. But there remains the underlying question: What are the expected results if all of the 186 patients living and traced at the *third* anniversary were followed to the fifth anniversary? Of these 186, there would be an expected 186/161 × 155 living and traced patients at the fourth anniversary, instead of the observed 155. Taking this fact into account, the expected numbers at the fifth anniversary are calculated by multiplying the observed numbers by

$$186/161 \times 155/149 = 1.1553 \times 1.0403 = 1.2019.$$

It is convenient to express the expected numbers at each anniversary as percentages of the total number of patients (205 patients). To obtain these percentages, the expected numbers are multiplied by 100/205. Accordingly, at each

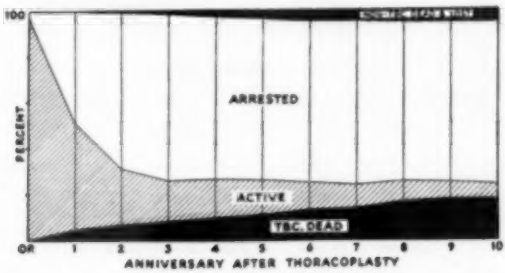


FIG. 1. Status at anniversary. Two hundred and five patients with thoracoplasty for parenchymal disease.

anniversary, the observed number of patients in each category, excepting the "incomplete," is multiplied by a correction factor which is 100/205 times the product of the provisional factors pertaining to that and all previous anniversaries.

The provisional and correction factors are entered in table 2, columns (*9*) and (*10*), respectively. At a specified anniversary, the expected percentages in columns (*11*) to (*15*) are obtained by multiplying the corresponding entry in columns (*2*) to (*6*) by the correction factor in column (*10*). The italicized entries in columns (*13*), (*14*), and (*15*) are the expected percentages of patients who *since operation* have died of tuberculosis, have died of nontuberculous causes, and have been lost, respectively. For example, at the fifth anniversary, the expected percentage of tuberculous deaths since operation is 4.39 + 1.95 + 1.95 + 1.69 + 1.17 = 11.15 per cent; the expected percentage of nontuberculous deaths is 0.49 + 0.56 + 0.59 = 1.64 per cent; the expected percentage of losses is 0.49 + 1.13 = 1.62 per cent. In figure 1 is shown graphically the values appearing in columns (*11*) and (*12*) as well as the italicized values in columns (*13*), (*14*), and (*15*). Straight lines connect the related points at successive anniversaries.

Columns (*11*) to (*15*) of table 2 give a qualified answer to the question pro-

posed at the outset. A direct answer has not been given because a few patients have been lost to follow-up. The manner in which these untraced patients are handled in the calculation depends partly on the aspect of tuberculosis which is being investigated.

To the administrator concerned with the problems of tuberculosis control, the percentage of lost patients in relation to time is of considerable interest. There is evidence (14) that a person with pulmonary tuberculosis of recent onset has a poorer prognosis than a person whose disease, although of the same extent, has remained stable for some time. Hence, patients lost early after diagnosis might be considered to constitute a greater public health problem than those lost later. Again, if losses are not evenly distributed throughout the period of study, some changes in programming may be indicated. The analysis of losses by the technique described above is most useful to the administrator.

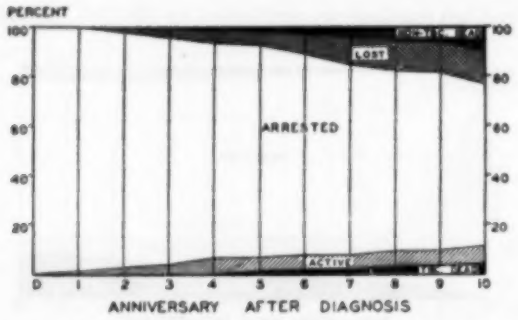


FIG. 2. Status at anniversary. Minimal arrested at diagnosis: 314 cases.

On the other hand, the loss of patients to follow-up does not permit the physician who treats tuberculosis to answer directly the proposed question. The gap in the after-history of the lost patients can be bridged by applying an assumption analogous to that made about "incomplete" patients, i.e., lost patients are assumed to be a random sample of the patients remaining under observation and therefore will have the same follow-up results. Whereas it is often possible to verify the assumption regarding "incomplete" patients, the assumption about lost patients is rarely subject to confirmation. In the present example, the stated assumptions about "incomplete" patients and lost patients are applied by adding each entry in column (*6*), table 2, to the corresponding entry in column (*8*), eliminating columns (*6*) and (*15*), and carrying out the calculations as previously. The procedure is illustrated in special reference table 2. As was noted above, the numerical results are identical to those obtained with the use of the life-table method (see special reference table 1).

Since the number of untraced patients in the thoracoplasty study is quite small, the assumptions about incomplete and lost patients were applied, for purposes of illustration, to clinical material containing more numerous losses (15).

The application of the assumption about "incomplete" patients only is illustrated in figure 2, while in figure 3 is illustrated the application of assumptions about both the lost and "incomplete" patients. As the number of losses shown in figure 2 increases at the later anniversaries, the reliability of the expected percentages shown in figure 3 decreases because of the growing weight given to the unconfirmed assumption about lost patients.

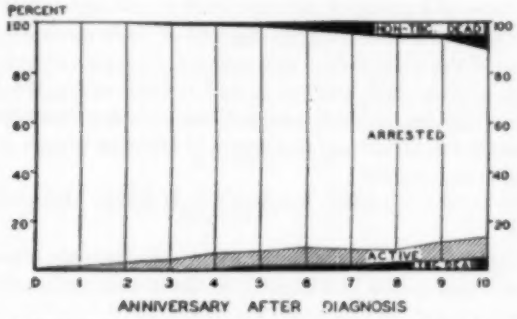


FIG. 3. Status at anniversary. Minimal arrested at diagnosis: 314 cases.

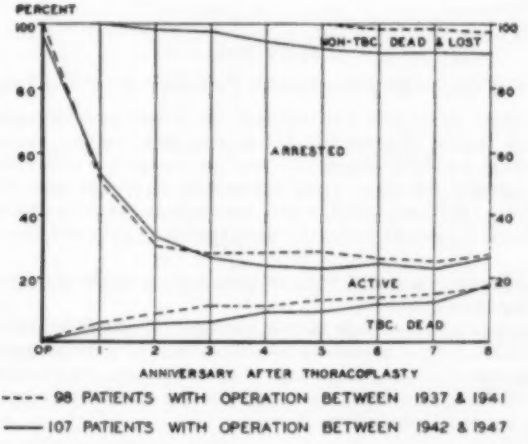


FIG. 4. Status at anniversary. Comparison of two groups of patients.

Since the assumption regarding "incomplete" patients is continually being applied, one should be alert to the conditions which invalidate it. Among these are (*a*) an effective change in therapy, and (*b*) variation in the clinical material admitted to study. Several means of appraising these conditions are available.

In the thoracoplasty study, the method described above was applied to those patients who were admitted during the first five years (1937 through 1941) and

then to those patients admitted during the last six years (1942 through 1947) (figure 4). Since the results compare closely, there appears to have been no significant variation in either clinical material or treatment. Alternatively, the results of the full study may be compared with the results based on data collected during a shorter period of follow-up.

SUMMARY

The clinical course of a group of patients with pulmonary tuberculosis is subject to a number of methods of analysis. Several of these methods make reasonably complete use of the clinical data and take full account of the following variables: the length of time each patient is under observation; the length of the interval between admission to study and a clinical event such as death, arrest of disease, or relapse; the duration and recurrence of arrest or relapse in each patient who remains under observation.

A modification of the life-table method which fulfills the above criteria is briefly described.

An alternative method of calculation is proposed which also meets the above criteria and which may prove quite useful to those unacquainted with the life-table technique.

Under identical sets of assumptions concerning "incomplete" and lost patients, the same numerical results are obtained by use of the life-table method and the alternative method.

SUMARIO

La Historia Posterior de la Tuberculosis Pulmonar: Métodos de Valuación

La evolución clínica de un grupo de tuberculosos pulmonares fué sometida a varios métodos de análisis. Varios de estos métodos utilizan bastante bien los datos clínicos y toman debidamente en cuenta las siguientes variables: tiempo que cada enfermo ha estado en observación; duración del plazo transcurrido entre el ingreso para estudio y algún acontecimiento clínico tal como fallecimiento, estacionamiento de la dolencia o recidiva; duración y recurrencia del estacionamiento o de la recaída en cada enfermo que permanece en observación.

Descríbese brevemente una modificación del método de las tablas de duración de la vida que cumple las pautas mencionadas.

Propónese un método alternativo de cálculo, que también cumple las pautas y que puede resultar bastante útil a los que no conocen las técnicas de las tablas de duración de la vida.

Con series idénticas de suposiciones relativas a los enfermos "incompletos" y perdidos de vista, obtiénense los mismos resultados numéricos con el método de las tablas de duración de la vida y con el método jalternativo.

RESUME

Histoire des suites de la tuberculose pulmonaire. Méthodes d'évaluation

Le cours clinique d'une série de cas de tuberculose pulmonaire est soumis à un certain nombre de méthodes d'analyse. Plusieurs de ces méthodes comportent l'emploi judicieux des données cliniques et tiennent strictement compte des variables suivantes: La durée de l'observation pour chaque malade; la durée de l'intervalle entre l'introduction dans l'étude et un événement clinique, tel que la mort, la stabilisation de la maladie ou la rechute; la

durée et la récurrence des rémissions ou des rechutes chez chacun des malades demeurésen observation.

Une modification de la méthode du tableau de survie, qui tient compte des critères ci-dessus, est décrite.

Une seconde méthode d'évaluation est offerte; elle satisfait également à ces critères et se montre très utile pour ceux non familiarisés avec la technique du tableau de survie.

Dans une série de postulats identiques concernant des cas "incomplets" ou perdus, les mêmes résultats numériques sont obtenus avec la méthode du tableau de survie et avec la seconde méthode.

Acknowledgment

We wish to thank Dr. Joseph Berkson of the Mayo Clinic, Dr. Philip E. Sartwell of the School of Hygiene and Public Health, Johns Hopkins University, and Dr. Mark Kac of the Department of Mathematics, Cornell University, for their helpful advice and suggestions.

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SPECIAL REFERENCE TABLE 1

LIFE-TABLE ANALYSIS OF THE RESULTS OF THORACOPLASTY ON 205 PATIENTS

YEARS AFTER OPERATION x TO x + 1	O_x	${}_1W_x$	${}_1d_x$	$q_{1}d_x$	$p_{1}d_x$	L_x	${}_1D_x$	PER CENT OF DEATHS BETWEEN x AND x + 1 DUE TO TUBERCULOSIS	CUM D_x − TB	CUM D_x − N	PER CENT OF LIVING ARRESTED AT x	SUBDIVISION OF L_x	
												Arrested	Active
0–1	205	0	9	0.0439	0.9561	1,000	44	100	44	0	2.4	24	976
1–2	196	1	4	0.0205	0.9795	956	20	100	64	0	51.0	488	468
2–3	191	0	5	0.0262	0.9738	936	25	80	84	5	73.3	686	250
3–4	186	27	4	0.0252	0.9748	911	23	75	101	11	80.6	734	177
4–5	155	6	3	0.0201	0.9799	888	18	66.7	113	17	80.6	716	172
5–6	146	5	4	0.0282	0.9718	870	25	75	132	23	82.9	721	149
6–7	137	10	1	0.0079	0.9921	845	7	100	139	23	85.4	722	123
7–8	126	16	5	0.0455	0.9545	838	38	80	169	31	87.3	732	106
8–9	105	26	2	0.0253	0.9747	800	20	100	189	31	88.6	709	91
9–10	77	19	0	0.0000	1.0000	780	0	—	189	31	89.6	699	81
10	58					780					91.4	713	67

O_x Number present in study at start of period x to x + 1.

${}_1W_x$ Number withdrawn from study between x and x + 1, by being lost from observation or termination of study.

${}_1d_x$ Number who died of all causes between x and x + 1.

$q_{1}d_x$ Probability of dying during this period $= \dfrac{{}_1d_x}{O_x - {}_1W_x}$.

$p_{1}d_x$ Probability of surviving during this period $= 1 - {}_1q_x$.

L_x Number remaining alive at time x out of an initial thousand, at these rates (each successive value obtained by multiplying L_{x-1} by $p_{1}d_{x-1}$).

${}_1D_x$ Number who died of all causes out of initial thousand $= L_x(q_{1}d_x)$.

Per cent of deaths between x and x + 1 due to tuberculosis $=$

$$\frac{\text{Number of deaths due to tuberculosis between x and x + 1}}{{}_1d_x} \times 100.$$

Cum D_x − TB Cumulative number of deaths due to tuberculosis out of initial thousand up to, and including, the current year (by addition) (tuberculous deaths found by multiplying ${}_1D_x$ by per cent of deaths due to tuberculosis).

Cum D_x − N Cumulative number of deaths due to causes other than tuberculosis up to, and including, the current year (by addition) (nontuberculous deaths found by multiplying ${}_1D_x$ by 100 minus per cent of deaths due to tuberculosis).

$$\text{Per cent of living arrested at x} = \frac{\text{number arrested at x}}{\text{total living at x}} \times 100.$$

Arrested L_x multiplied by per cent of living arrested at x.

Active L_x minus number arrested.

SPECIAL REFERENCE TABLE 2

PATIENTS TREATED BY THORACOPLASTY 1938–1947 CLASSIFIED BY STATUS AT EACH ANNIVERSARY

(1)	(2)	(3)	(4)		(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
ANNIVERSARY	LIVING AT ANNIVERSARY		DIED SINCE PREVIOUS ANNIVERSARY		TOTAL	LOST AND INCOMPLETE	FACTORS		EXPECTED PERCENTAGES			
	Arrested	Active	Tuberculosis	Nontuberculous Disease			Provisional	Correction	Arrested	Active	Died of Tuberculosis	Died of Nontuberculous Disease
0	5	200	0	0	205	0	1.0000	0.4878	2.44	97.56	0	0
1	100	96	9	0	205	0	1.0000	0.4878	48.78	46.83	4.39	0
											4.39	
2	140	51	4	0	195	1	1.0051	0.4903	68.64	25.01	1.96	0
											6.35	
3	150	36	4	1	191	0	1.0000	0.4903	73.55	17.65	1.96	0.49
											8.31	*0.49*
4	125	30	3	1	159	27	1.1698	0.5736	71.70	17.21	1.72	0.57
											10.03	*1.06*
5	121	25	2	1	149	6	1.0403	0.5967	72.20	14.92	1.19	0.60
											11.22	*1.66*
6	117	20	3	1	141	5	1.0355	0.6179	72.29	12.36	1.85	0.62
											13.07	*2.28*
7	110	16	1	0	127	10	1.0787	0.6665	73.32	10.66	0.67	
											13.74	*2.28*
8	93	12	4	1	110	16	1.1455	0.7635	71.01	9.16	3.05	0.76
											16.79	*3.04*
9	69	8	2	0	79	26	1.3291	1.0148	70.02	8.12	2.03	
											18.82	*3.04*
10	53	5	0	0	58	19	1.3276	1.3472	71.40	6.74		
											18.82	*3.04*

(*1*) Number of years after thoracoplasty.

(*2*) Number of living patients with arrested disease at anniversary.

(*3*) Number of living patients with active disease at anniversary.

(*4*) Number who died of tuberculosis since previous anniversary.

(*5*) Number who died of causes other than tuberculosis since previous anniversary.

(*6*) Number at anniversary, sum of columns (*2*) to (*5*) inclusive.

(*7*) Number of incomplete and lost patients at anniversary.

(*8*) Provisional factor for anniversary $= \dfrac{\text{column } (6) + \text{column } (7)}{\text{column } (6)}$.

(*9*) Correction factor for anniversary = column (*8*) × correction factor for previous anniversary. The correction factor for anniversary 0 is 100/205 = 0.4878.

(*10*) Expected percentage of living patients with arrested disease at anniversary: column (*2*) × column (*9*).

(*11*) Expected percentage of patients with active disease at anniversary: column (*3*) × column (*9*).

(*12*) Expected percentage of patients dead of tuberculosis at anniversary: column (*4*) × column (*9*). Cumulative percentages in italics.

(*13*) Expected percentage of patients dead of causes other than tuberculosis at anniversary: column (*5*) × column (*9*). Cumulative percentages in italics.

COMBINED REST AND EXERCISE IN THE TREATMENT OF MINIMAL TUBERCULOSIS[1]

A Follow-Up Study of One to Thirty Years

EDWARD N. PACKARD AND PAUL F. FLYNN

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INTRODUCTION

Combined rest and exercise were formerly prescribed for patients in the minimal stage of pulmonary tuberculosis with mild or no constitutional symptoms. In recent years, however, any form of exercise for patients in this category has been regarded as injurious. As a consequence, bed rest has, in general, replaced combined rest and exercise. In many instances, strict bed rest which excludes bathroom privileges is employed, and at times even writing or listening to the radio is not permitted. The duration of this form of treatment is usually from three to six months, except in those instances where stabilization of the lesion is deemed essential before allowing the patient out of bed, in which case the treatment may be prolonged to a year or even longer (1).

It seemed to the writers, from casual observations covering a period of many years, that the results with bed rest were not superior to those obtained in earlier days by rest in reclining chairs combined with graduated walking exercise. Such impressions often prove fallacious, however, and for this reason the one- to thirty-year follow-up observations have been studied for 152 patients with uncomplicated active minimal tuberculosis who were treated by combined rest and exercise at the Trudeau Sanatorium during the years 1921 to 1929, inclusive.

Review of Literature

The first proponent of strict bed rest for the "early"[2] tuberculous lesion was Amberson (2) who, in 1937, reported his observations of more than 100 patients treated by strict bed rest for two to four months. In a follow-up period of one to ten years, a "lasting cure" was obtained in approximately 90 per cent of the cases. The measure also appeared to prevent the "early" lesion from progressing, since "the majority of early infiltrations developing in young people progress and undergo excavation if they are not promptly and properly treated."

The experience of Childress (3) was less favorable. In a series of 45 patients in the "early" stage, on strict bed rest for an average period of six months, he found that the disease had progressed to the advanced stage in no less than 10 instances (22 per cent). Five lesions progressed while the patients were on bed rest, and 5 reactivated and progressed after first responding favorably to a period of hospitalization and bed rest. Two patients in this group died of tuberculosis.

The study of Badger and Ayvazian (4) included 45 nurses in training who presented

[1] Aided by a grant from the Lawrason Brown Memorial Fund, Saranac Lake, New York.

[2] The "early" lesion is located in the upper part of the lung, is usually not more than 3 cm. in diameter, and is early in the sense that it is discovered within a year by serial roentgenograms.

"early" lesions with a follow-up period ranging from five to fifteen years. Thirty-two of the 45 nurses in this series received bed rest with bathroom privileges for a period of five and one-half months. The disease was arrested in 26 patients (81 per cent); 5 were still under observation; one died (2.2 per cent). The remaining 13 nurses refused treatment and were permitted to continue their nursing duties under medical supervision. Relapses occurred in 3 of these, who were then treated by modified bed rest, but ultimately the disease was arrested in all instances.

Bobrowitz, Hurst, and Martin (5), in a study of 220 minimal cases of "all types," found an accumulative five-year progression rate of 42 per cent. Of 66 patients with "exudative and exudative-productive lesions" who were treated by complete bed rest, there was a five-year accumulative progression rate of 55 per cent. In an earlier article (1942), Bobrowitz (6) states that "from 75–80 per cent of the minimal cases resolve or fibrose and become stable with bed rest and remain well." This study covered a period of six years.

Heller (7), reporting on 55 patients "with small unilateral active, noncavitary tuberculous lesions" who were observed from one to five and one-half years, found that, of 34 who were treated by bed rest, the disease in 17 patients (50 per cent) relapsed. In the latter group, no deaths occurred during the period of observation.

Paine (8), in a study of 103 patients with minimal tuberculosis confined to the apex of the lung, found that the progression rate (by serial roentgenograms) was 57 per cent for those treated with bed rest alone and 19 per cent for those treated with collapse therapy. The end results of all cases five to twenty-two years after admission to the Sanatorium showed disease arrested or apparently cured in 94 patients and 2 dead from tuberculosis.

Mitchell (9) found a 27.6 per cent relapse rate in 589 patients with active minimal pulmonary tuberculosis treated by modified bed rest during a projected twenty-year follow-up period. There was a 5 per cent tuberculosis mortality rate.

Reisner and Downes (10), in 1945, published a statistical analysis of 469 white and nonwhite individuals with minimal pulmonary tuberculosis whose disease was discovered in most instances by routine roentgenographic examinations made in the outpatient clinics in New York City. Seventy-six per cent of the entire group denied symptoms of tuberculosis. The lesions of 220 patients were classified by the writers as "exudative-productive" and "about one half" progressed during the five-year period of observation. Sixty per cent of this group had institutional care but the exact form of treatment was not stated. The mortality rate at the end of five years was approximately 2 per cent.

The references cited above indicate that there is considerable disparity in the relapse rates (22 to 57 per cent) of patients with minimal pulmonary tuberculosis treated by bed rest. This is due, in part, to differences in the definition of the term "relapse" or "progression." Some observers base their opinion entirely on an extension of the shadows seen in the roentgenogram; others depend upon the clinical findings; and some, on a combination of both. Regardless of the numbers of percentages of relapses, the mortality rate is approximately the same in all series, namely, 2 per cent up to the tenth year after the initial discovery of the disease.

MATERIAL

The clinical records, roentgenograms, and the information given in the yearly questionnaires of 467 patients admitted to the Trudeau Sanatorium with the

classification of minimal tuberculosis during the years 1921 to 1929, inclusive, were reviewed for the present study.

Patients with pleurisy with effusion or extrapulmonary complications were excluded from the study, as well as those whose roentgenograms disclosed old and healed lesions as determined by dense, sharply circumscribed, or stringlike shadows.

The object was to obtain as "early" cases as possible. It was not possible to estimate the duration of the disease by serial roentgenographic examinations, for in those days, unlike the present, it was the exception for evidence of the disease to be first revealed by this means. All patients sought medical advice because of symptoms, fatigue, loss of weight, cough, expectoration, hemoptysis, or pains in the chest. One hundred and fifty-two patients were found whose initial symptoms appeared within one year of their admission to the Sanatorium and who had adequate follow-up reports following discharge.

The roentgenographic examinations showed unmistakable evidence of disease in all cases. The disease was located, with few exceptions, in the upper part of the lung, and the sum total of the area of the shadow cast by lesions varied from 1 to 4 cm. in diameter. The shadows were predominantly soft and mottled in appearance. In the majority of instances, these shadows diminished in extent during the patient's residence in the Sanatorium.

In this group of 152 white patients, there were 82 females and 70 males. The average age was twenty-seven years, the extremes being seventeen and forty-six years. Acid-fast bacilli were present at some time in the sputum by direct smear in 65 (43 per cent) of the patients. Cultures of the sputum were not routinely employed in those years.

TREATMENT

The patients were first admitted to the reception pavilion for an observation and examination period of two to three weeks. While there the patients, with a few exceptions, rested, fully dressed, in reclining chairs, out of doors, and walked to the dining room in an adjacent building for their meals. In winter they wore heavy overcoats and overshoes which they put on and took off at meal time—in itself, considerable exercise. This exercise at an average of three and one-half weeks after admission was materially increased when the patients were transferred to the ambulant cottages located on the sides of a rather steep hill and 50 to 220 yards from the dining room. In general, they were allowed fifteen minutes' exercise twice daily in addition to walking to their meals. The period was gradually increased to two or more hours daily by the fourth or fifth month.

During their entire residence, ranging from three to twelve months (with an average period of 6.4 months), the patients (unless they became ill or suffered a relapse) remained dressed during the day and rested in reclining chairs out of doors from 9 a.m. to 5 p.m. except for the exercise program outlined for them.

A few patients were slower in attaining full exercise status or did not reach the hour twice a day. Four patients were admitted to the infirmary and 2 were sent to rest cottages because of extensions of disease.

The majority of patients in the Sanatorium during the years 1921–1929 had roentgenograms of the chest made upon admission, at the end of three months, and on discharge.

Tubercle bacilli were first found in the sputum of 39 patients after their admission to the Sanatorium. However, the finding of these microorganisms in no way altered the patients' graduated exercise, in striking contrast to the present day when ambulant patients are often returned to bed upon the discovery of tubercle bacilli in the sputum or gastric contents.

RESULTS

In table 1 an arrangement is presented of the 152 cases in this series into "No Relapse" and "Relapse" groups and the results of treatment by combined rest and exercise up to thirty years after discharge.

TABLE 1

RESULTS IN 152 CASES OF ACTIVE MINIMAL TUBERCULOSIS TREATED BY COMBINED REST AND EXERCISE AT THE TRUDEAU SANATORIUM 1921–1929, INCLUSIVE

	YEAR OF LAST REPORT FOLLOWING DISCHARGE							
	1-5	6-10	11-15	16-20	21-25	26-30	Totals	
							Number	Per Cent
No Relapse Group								
Well and working	2	3	6	5	57	38	111	73.2
Nontuberculous deaths			1		5	1	7	4.6
Relapse Group								
Well and working	1			2	12	2	17	11.2
Disabled by tuberculosis						3	3	1.9
Dead of tuberculosis	2	1	6	2	1		12	7.8
Dead of other causes			1		1		2	1.3
Total							152	100.0

Of the total number studied, 128 (84 per cent) were well and working when last heard from. One hundred and nine (72 per cent) were known to be well and working twenty to thirty years after leaving the Sanatorium. Three patients discharged in 1929 were alive in 1950 but were disabled by tuberculosis.

Based on reports from families, physicians, or hospitals, there were 12 deaths from tuberculosis (7.8 per cent) during the thirty-year period; 3 occurred within eleven years after discharge (2 per cent). In addition, 9 patients (6 per cent) died of other causes fourteen to thirty years after discharge (4 from neoplastic disease, 2 from accidents, 2 from cardiovascular disease, and one from cirrhosis of the liver). The tuberculosis in these persons was clinically inactive at the time of death as judged by the yearly report.

Thirty-four patients suffered primary relapses (22.4 per cent). Six of these relapses occurred during the patients' residence in the Sanatorium and 28 in

subsequent years up to and including the twelfth year after discharge, as shown in table 2. A relapse was diagnosed by clinical signs and symptoms, confirmed by the roentgenogram. Treatment of the relapse patients consisted of bed rest, pneumothorax in 10 cases, thoracoplasty in 3 (one also had a lobectomy), and 5 had phrenic nerve operations.

TABLE 2

ONE HUNDRED AND FIFTY-TWO PATIENTS TREATED BY COMBINED REST AND EXERCISE, 1921–1929

Number of Patients and Year of First Relapse Following Admission to the Sanatorium

	Years Following Discharge						
	IN SANATORIUM	1–5	6–10	11–15	16–30	TOTAL	
						Number	Per Cent
Number whose disease relapsed	6	17	8	3	0	34	22.4

DISCUSSION

The 152 patients in the present series sought medical advice because they had such symptoms as hemoptysis, fatigue, cough, expectoration, and chest pains, which is in marked contrast to the present day when minimal tuberculosis is usually discovered by means of the roentgenogram and the majority of patients are asymptomatic.

The Trudeau group here reported is representative of those patients whose lesions have advanced beyond the "early" stage to the stage when symptoms manifest themselves, although the extent of the lesions is within the National Tuberculosis Association classification of "minimal."

According to the present-day standards, these patients were ambulatory from the start of treatment; yet the end results, after a long term of years, compare favorably with the results reported of patients in the same category who were treated by weeks and months of bed rest.

The results of the present study are in general accord with the observations of Bray (11), who prescribed combined rest and exercise as practiced at the Trudeau Sanatorium in former years. He found in a series of 67 patients in the "early" stage of the disease that the lesions in 16 (24 per cent) progressed, an incidence approximately the same as Childress found in the above-mentioned series of 45 patients treated by strict bed rest. Bray's patients were followed for periods ranging from one to fourteen years.[3] At no time previous to their admission, during their stay, or subsequent to their discharge did they receive treatment by bed rest, but they rested in reclining chairs except for prescribed periods of walking, making their beds, and sweeping their rooms.

Bray also drew attention to the discharge classification of 360 patients who were admitted during the years 1939 to 1942, inclusive, when the age of the dis-

[3] Unpublished data.

ease was undetermined, of whom 97 received an average of four months' strict bed rest before admission to the hospital and 263 had not received strict bed rest before admission. While in the hospital (an average of seven months) they were ambulant patients on supervised exercise. The classification at discharge showed practically the same percentage in both groups:

	97 PATIENTS WHO HAD RECEIVED STRICT BED REST	263 PATIENTS WHO HAD NOT RECEIVED STRICT BED REST
	per cent	*per cent*
Arrested	71.1	79.8
Apparently arrested	12.2	11.8
Active or quiescent	16.5	8.4

In general, it is safe to state that being confined to bed without bathroom privileges for a period of months is a frustrating experience for a patient in the minimal stage of the disease who looks and feels well and presents mild or no constitutional symptoms. Aside from the marked loss of muscular tone, the mental as well as the physiologic processes of the body are disturbed and the period of rehabilitation is protracted. These disadvantages have been recognized by many observers (12, 13, 14), yet the treatment prevails because any form of exercise for patients in this category is regarded as detrimental.

The present study indicates that the end results of the treatment of minimal tuberculosis by combined rest and exercise are comparable with the results obtained by strict or modified bed rest as reported in the literature.

Until more tangible evidence is forthcoming in support of the claims advanced for strict bed rest as a preventive and curative measure, the formerly established regimen of combined rest and exercise is to be preferred for those patients with minimal pulmonary tuberculosis who present only mild or no constitutional symptoms.

SUMMARY

The records of 152 patients with active minimal pulmonary tuberculosis who were admitted to the Trudeau Sanatorium during the years 1921 to 1929, inclusive, and treated by combined rest and exercise were reviewed in 1951–1952. One hundred and twenty-eight (84 per cent) were well and working when last heard from. Of these, 109 (72 per cent) were known to be well and working twenty to thirty years after discharge from the Sanatorium.

Thirty-four patients (22.4 per cent) suffered initial relapses. Seventeen recovered and were working in 1950. Three were still disabled by tuberculosis. Twelve of the group of 152 patients died of tuberculosis (7.8 per cent). Nine patients (6 per cent) died of causes other than tuberculosis.

Patients in the minimal stage of the disease who had mild or no constitutional symptoms remained dressed during the day, sat in reclining chairs, out of doors, and at stated times engaged in graduated exercises. The results of this form of treatment compare favorably with the results obtained by strict and modified bed rest as reported in the literature.

SUMARIO

El Descanso y el Ejercicio Combinados en el Tratamiento de la Tuberculosis Mínima

Este repaso, realizado en 1951–1952, comprendió los protocolos de 152 enfermos que tenían tuberculosis pulmonar mínima activa y que fueron admitidos en el Sanatorio Trudeau durante los años 1921 a 1929, inclusive, y tratados a base de reposo y ejercicio combinados. Ciento veintiocho (84 por ciento) se hallaban bien y trabajando cuando se supo la última vez de ellos. De éstos, 109 (72 por ciento) se sabe que que estaban bien y trabajando de veinte a treinta años después de darlos de alta del Sanatorio.

Treinta y cuatro enfermos (22.4 por ciento) experimentaron recidivas iniciales. Diecisiete se repusieron y estaban trabajando en 1950. Tres estaban todavía incapacitados por la tuberculosis. Doce (7.8 por ciento) del grupo de enfermos de 1952 murieron de tuberculosis. Nueve (6 por ciento) fallecieron de causas distintas de la tuberculosis.

Los enfermos que se hallaban en la fase mínima de la enfermedad, que no tenían síntomas orgánicos o, si los tenían, eran leves, se vestían durante el día, se recostaban en sillones al aire libre y, a ciertas horas, se dedicaban a ejercicios graduados. Los resultados de esa forma de tratamiento se comparan favorablemente con los obtenidos por medio del reposo en cama rígido y modificado, según constan en la literatura.

RESUME

Repos et exercice combinés dans le traitement de la tuberculose a minima

Les dossiers de 152 patients atteints de tuberculose pulmonaire *a minima*, hospitalisés au Sanatorium Trudeau au cours des années 1921 à 1929, inclusivement, et soumis au traitement exercice-repos, ont été examinés en 1951–1952. Aux dernières nouvelles, 128 malades (84%) étaient bien portants et travaillaient. Parmi ceux-ci, 109 malades (72%) étaient bien portants et travaillaient vingt à trente ans après avoir quitté le sanatorium.

Trente-quatre malades (22, 4%) ont présenté des rechutes initiales. Dix-sept ont guéri et travaillaient en 1950. L'invalidité par tuberculose persistait chez trois malades. Douze malades de la série 1952 sont morts de tuberculose (7, 8%). Neuf malades (6%) ont succombé à d'autres affections.

Les patients au stade minimum de la maladie, dont les lésions organiques étaient légères ou inexistantes, s'habillaient durant la journée, s'allongeaient sur des chaises longues et s'adonnaient à des exercices progressifs à des heures déterminées. Les résultats de cette forme de traitement soutiennent favorablement la comparaison avec ceux obtenus par le repos au lit strict ou modifié, tel qu'il est décrit dans la littérature médicale.

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DAILY OXYTETRACYCLINE (TERRAMYCIN) AND INTERMITTENT STREPTOMYCIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

An Investigation of the Administration of Two Grams of Oxytetracycline Daily

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INTRODUCTION

In a previous study of 66 patients with pulmonary tuberculosis, the administration of 5 gm. of oxytetracycline (Terramycin[2]) orally per day together with 2 gm. of streptomycin intramuscularly every third day for 120 days afforded clinical, roentgenographic, and bacteriologic responses as beneficial as the proved regimen of streptomycin and para-aminosalicylic acid (PAS) (1).

Mild, but troublesome, gastrointestinal tract symptoms were experienced by many patients on 5 gm. of oxytetracycline per day. Consequently, a second study was started in April, 1952, with the hope that 2 gm. of oxytetracycline in combination with streptomycin would still delay the emergence of streptomycin-resistant tubercle bacilli and minimize untoward gastrointestinal tract symptoms.

METHOD OF STUDY

Twenty patients with active pulmonary tuberculosis were selected for this study in conformity with the following criteria: no previous antituberculous drug therapy; disease of greater than minimal extent; and bacteriologically demonstrated infection.

An attempt was made to select patients whose disease type suggested that they might still yield positive cultures after 120 days of combined therapy.

The drug regimen consisted of 2 gm. of oxytetracycline (Terramycin) orally daily and 2 gm. of streptomycin intramuscularly every third day. The analysis was made after 120 days of therapy; however, it is emphasized that drugs were continued in all cases for longer periods of time.

The patients selected consisted entirely of males from twenty to seventy-eight years old, the average being thirty-five years. Thirteen were white, and 7 were nonwhite. Fourteen (70 per cent) had moderately advanced, and 6 (30 per cent) had far advanced, disease. All but one of the 20 patients had clearly demonstrated cavities by postero-anterior or apical roentgenograms at the start of therapy. The disease was predominately exudative and caseous in 15 patients, while 5 patients exhibited a combination of caseous, exudative, and fibrotic disease.

Roentgenographic trend and treatment response were evaluated by a panel of five

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[1] From the Tuberculosis Section and the Research and Development Branch, Fitzsimons Army Hospital, Denver 8, Colorado.

[2] The Terramycin hydrochloride used in this study was kindly supplied through the courtesy of Chas. Pfizer & Co., Inc., Brooklyn, New York.

physicians on a 5-point scale as follows: marked improvement, moderate improvement, slight improvement, no change, and worsening.

The presence of cavities and their changes during therapy were not considered factors in judging the degree of response.

Clinical, roentgenographic, and bacteriologic evaluations were made, comparing the findings at the start of therapy with those after 120 days. Untoward symptoms related to the drugs themselves were recorded.

Specimens of sputum or gastric washings were examined at two-week intervals using conventional smear and culture techniques. Drug-susceptibility studies were performed on all positive cultures, using American Trudeau Society medium containing 0, 1, 10, and 100 γ of streptomycin per ml. and oleic-acid-albumin-agar medium containing 0, 6.25, 12.5, 25, 50, 100, and 200 γ of oxytetracycline per ml. After seven to fourteen days of incubation, growth on the drug-containing medium was evaluated by comparison with the control. In accord with previous studies from this hospital, cultures which showed growth in the presence of 10 γ of streptomycin or 25 γ of oxytetracycline per ml. equal to that on the control were arbitrarily called "resistant."

Sputum and feces were collected from these patients at two-week intervals prior to and during therapy. Specimens were diluted in sterile saline and cultured directly on blood and eosin-methylene blue agar containing 0 and 100 γ of oxytetracycline per ml. The saline dilutions were then digested in a streptomycin and penicillin mixture and cultured on Sabouraud's dextrose agar containing 0 and 100 γ of oxytetracycline per ml. The blood and eosin-methylene blue plates were incubated at 37°C. for twenty-four hours and the Sabouraud's for five to seven days at room temperature. Predominating organisms were identified by the usual bacteriologic procedures and their numbers estimated.

During the study period all patients received no other form of antituberculous treatment except bed rest.

EVALUATION

Clinical: After 120 days of streptomycin and oxytetracycline (Terramycin), 8 of 20 patients had improvement of cough, while 8 of 13 had a significant reduction of sputum volume. Worsening did not occur in either of these categories.

Twelve of the 20 patients had weight gain (in excess of 5 pounds), 8 showed no change (plus or minus 5 pounds), and there was no instance of weight loss (in excess of 5 pounds).

Roentgenographic: At the start of therapy one patient had regressive, one had progressive, and 18 had stationary, disease as determined by pretreatment roentgenograms. Of the 20 patients, all manifested some degree of roentgenographic improvement. One had marked improvement, 7 had moderate improvement, and 12 had slight improvement. Cavities were present in 19 of the 20 patients at the start of therapy; 2 of these patients no longer exhibited cavities after 120 days.

Bacteriologic: Thirteen of the 20 patients had sputum "conversion" (negative for *M. tuberculosis* for three months or longer) on completion of 120 days of therapy. Seven patients continued to discharge tubercle bacilli. One strain was resistant to streptomycin; the other 6 were drug susceptible. Oxytetracycline resistance was not encountered.

All patients had essentially normal fecal and respiratory flora prior to chemotherapy. Within a few days after the initiation of drug treatment, the major changes in microbial populations had occurred and little variation was observed as long as oxytetracycline was continued.

Clinical toxicity: Approximately one-half of the 20 patients experienced one or more undesirable side effects believed to be attributable to oxytetracycline during 120 days of drug administration. The description and incidence of these reactions are listed in table 1. In general, the reactions were transient and mild and, in the 2 patients in whom nausea and vomiting tended to persist, tincture of belladonna administered to tolerance brought complete relief. Diarrhea tended to be persistent in one patient, but was controlled by paregoric. Of considerable

TABLE 1

TOXICITY DURING 120 DAYS OF OXYTETRACYCLINE (TERRAMYCIN) THERAPY, 2 GM. DAILY
20 PATIENTS

TYPE OF REACTION	NUMBER OF PATIENTS	PER CENT
Anorexia	4	20
Nausea	2	10
Vomiting	1	5
Diarrhea	8	40
Bulky or mushy stool	4	20
Sore tongue	3	15
Rash	0	0
Pruritis ani	10	50
Cheilosis	3	15

TABLE 2

ABNORMAL SPUTUM FLORAL CHANGES IN 16 PATIENTS TREATED 120 DAYS WITH 2 GM. OF OXYTETRACYCLINE (TERRAMYCIN) DAILY

PREDOMINANT FLORAL CHANGES	NUMBER OF PATIENTS
Coliform bacilli (resistant to oxytetracycline)	1
Coliform bacilli (susceptible to oxytetracycline)	1
Hemolytic *Staphylococcus aureus* (resistant to oxytetracycline)	4
Beta *Streptococcus hemolyticus* (resistant to oxytetracycline)	6
Beta *Streptococcus hemolyticus* (susceptible to oxytetracycline)	3
Enterococci (susceptible to oxytetracycline)	1
Enterococci (resistant to oxytetracycline)	1
Yeast-like fungi	8
Pseudomonas aeruginosa (susceptible to oxytetracycline)	1

interest was the occurrence of mild, transient sore tongue in 3 patients, and of cheilosis in 3 patients. Transient, mild anal pruritis was noted in one-half of the patients.

The finding of the following organisms predominating in the sputum were considered abnormal: Coliform group bacilli, hemolytic *Staphylococcus aureus*, (resistant to oxytetracycline), *Streptococcus hemolyticus*, *Pseudomonas aeruginosa*, and increased numbers of yeast-like fungi. Sixteen of 19 patients studied for floral changes yielded one or more abnormalities (table 2). However, clinically or roentgenographically there were no correlative changes with these abnormalities.

The finding of increased numbers of yeast-like fungi and *Proteus* bacilli in the stool was considered abnormal. Ten of 19 patients had one or more abnormal floral changes. Seven of these 10 had one or more of the following correlative symptoms: diarrhea, bulky or mushy stools, sore tongue, pruritis ani, or cheilosis. Table 3 correlates change in fecal flora with untoward symptomatology. Seven of 19 patients had one or more of the above-mentioned symptoms without fecal floral changes by the methods employed, although all stools were characterized by increased numbers of enterococci.

TABLE 3

ABNORMAL FECAL FLORAL CHANGES AND CORRELATIVE SYMPTOMATOLOGY IN 10 PATIENTS TREATED 120 DAYS WITH 2 GM. OF OXYTETRACYCLINE (TERRAMYCIN) DAILY

PATIENT	SYMPTOMATOLOGY	PREDOMINANT FLORAL CHANGES*
1	Diarrhea, sore tongue, pruritis ani, and cheilosis	*Proteus* (resistant to oxytetracycline); yeast-like fungi
2	Diarrhea, sore tongue, and pruritis ani	Yeast-like fungi
3	Bulky, mushy stools, and pruritis ani	Yeast-like fungi
4	Diarrhea and pruritis ani	Yeast-like fungi
5	Pruritis ani and cheilosis	Yeast-like fungi
6	Pruritis ani	*Proteus* (resistant to oxytetracycline)
7	Sore tongue	Yeast-like fungi
8	None	Yeast-like fungi
9	None	*Proteus* (resistant to oxytetracycline)
10	None	Yeast-like fungi

* All stools were characterized by increased numbers of enterococci, resistant in all cases to oxytetracycline.

COMMENT

With prolonged drug therapy becoming increasingly important in the treatment of tuberculosis, possession of a variety of effective antituberculous drugs is advantageous. This is especially important as clinical or bacteriologic resistance to current drug regimens becomes evident. In view of this fact and the feasibility of "triple drug" therapy, as well as the excellent patient acceptance of oxytetracycline (Terramycin) in moderate dosage over para-aminosalicylic acid, oxytetracycline may become increasingly more important in the drug therapy of tuberculosis. Thus, further investigation of oxytetracycline seemed justifiable. Because of the gastrointestinal irritability at the 5 gm. dosage level, an attempt was made in the present series to study the effect of oxytetracycline by employing 2 gm. daily. It was also believed to be advisable to compare this regimen with 1 or 2 gm. of streptomycin every third day alone (table 4). Drug-resistant studies were performed by the same laboratory and by the same methods for comparative purposes.

The clinical improvement obtained in the present study was comparable to that of other drug regimens employed at Fitzsimons Army Hospital. One factor of importance, however, was the failure of any patient to lose weight on the 2

gm. oxytetracycline dosage level, in contrast to 19.7 per cent of patients who lost 5 or more pounds in a 120-day period while receiving 5 gm. of oxytetracycline daily (1). It is believed that this is due to the decrease in gastrointestinal symptoms associated with reduced oxytetracycline dosage.

The roentgenographic response in this small group of patients was observed to be essentially similar to that of the group of patients who received the 5 gm. oxytetracycline-streptomycin regimen and superior to the response of those who received streptomycin alone every third day.

TABLE 4

COMPARATIVE 120-DAY EVALUATION OF INTERMITTENT STREPTOMYCIN AND INTERMITTENT STREPTOMYCIN AND OXYTETRACYCLINE (TERRAMYCIN) DAILY

	1 TO 2 GM. OF STREPTOMYCIN EVERY THIRD DAY	2 GM. OF OXYTETRACYCLINE DAILY AND 2 GM. OF STREPTOMYCIN EVERY THIRD DAY	5 GM. OF OXYTETRACYCLINE DAILY AND 2 GM. OF STREPTOMYCIN EVERY THIRD DAY
Number of patients	97	20	66
Symptomatic improvement	65	14	36
Roentgenographic change			
Improved			
All degrees	60	20	64
Slight	42	12	31
Moderate and marked	27	8	33
No change	24	0	2
Worsened	4	0	0
Cavity lost to view	16	2	7
Bacteriology			
Negative for *M. tuberculosis*	36	13	51
Positive for *M. tuberculosis*	61	7	15
Resistant to 10 γ of streptomycin per ml.	32	1	0
Resistant to 10 γ of PAS per ml.	—	0	0
Resistant to 25 γ of oxytetracycline per ml.	—	0	0

Note:—Drug-resistance studies performed by same laboratory and by same methods for comparison.

Oxytetracycline in a 2 gm. daily dose failed to prevent completely the emergence of streptomycin-resistant tubercle bacilli. This phenomenon occurred in one of the 7 patients whose sputum remained positive after 120 days of therapy. This is slightly inferior to the 5 gm. oxytetracycline with intermittent streptomycin regimen but definitely superior to streptomycin alone every third day.

Undesirable reactions to 2 gm. of oxytetracycline daily were milder, less persistent, and occurred in fewer patients than in those who received 5 gm. daily. This was particularly evident in the incidence of anorexia, vomiting, and nausea (2). The absence of weight loss by any patient further emphasizes

this point. Pruritis ani, although occurring in 50 per cent of the patients, was of such minor degree that none of the patients voluntarily complained of this symptom, and it was brought out only after careful questioning by the physician. Cheilosis and sore tongue were each found to occur in 15 per cent of this series but were not noted in the 5 gm. dosage group. The significance of these side-effects is not clear. Sputum and fecal microfloral studies revealed marked changes in a high percentage of the patients studied. Sputum microfloral changes could not be correlated with any clinical or roentgenographic changes. There appeared to be a suggestive, but not definite, correlation between fecal microfloral changes and symptomatology.

Patient acceptance of the lower dosage regimen of oxytetracycline was superior to that observed with the 5 gm. dosage schedule.

SUMMARY

Twenty patients with active pulmonary tuberculosis were selected to receive treatment for 120 days with 2 gm. of oxytetracycline (Terramycin) orally daily and 2 gm. of streptomycin intramuscularly every third day.

Clinical and roentgenographic improvement closely paralleled that observed with intermittent streptomycin and oxytetracycline, 5 gm. daily, but was superior to that observed with streptomycin alone every third day.

Undesirable reactions to 2 gm. daily were milder, less persistent, and less frequent than with the 5 gm. oxytetracycline regimen.

Fecal and sputum microfloral changes were studied. An attempt was made to correlate these findings with clinical toxicity.

Oxytetracycline in this dosage schedule failed to afford complete protection against the emergence of streptomycin-resistant tubercle bacilli, although this regimen showed superiority to that employing streptomycin alone, 1 to 2 gm. every third day.

In using oxytetracycline in combination with streptomycin in the therapy of pulmonary tuberculosis, 5 gm. of oxytetracycline daily would appear to be superior to that of 2 gm. daily. It is likely, however, that the optimal dosage of oxytetracycline lies somewhere between 2 and 5 gm. daily.

Daily oxytetracycline in combination with intermittent streptomycin is an acceptable and useful drug regimen for the treatment of active pulmonary tuberculosis.

SUMARIO

L'Oxitetraciclina (Terramicina) Diaria y la Estreptomicina Intermitente en el Tratamiento de la Tuberculosis Pulmonar: Investigacion de la Administracion de Dos Gramos Diarios oxytetraciclina

Veinte enfermos con tuberculosis pulmonar activa fueron escogidos para recibir tratamiento durante 120 días con 2 gm. de Terramicina por vía bucal diariamente y 2 gm. de estreptomicina intramuscularmente cada tres días.

La mejoría clínica y roentgenográfica paraleló muy de cerca la observada con la estreptomicina y la oxitetraciclina administradas intermitentemente, 5 gm. diarios, yero fué superior a la observada con la estreptomicina sola administrada cada tres días.

Las reacciones adversas a 2 gm. diarios fueron más leves y menos persistentes y frecuentes que con el régimen de 5 gm. de oxitetraciclina.

Se estudiaron las alteraciones en la microflora de las heces y del esputo, tratando de correlacionar esos hallazgos con la toxicidad clínica.

Con el esquema posológico mencionado, la oxitetraciclina no proporcionó protección absoluta contra la aparición de bacilos tuberculosos estreptomicinorresistentes, aunque dicho régimen se mostró superior al que emplea estreptomicina sola, 1 ó 2 gm. cada tres días.

Al usar oxitetraciclina junto con estreptomicina en la terapéutica de la tuberculosis pulmonar, parece que 5 gm. diarios de oxitetraciclina son superiores a 2 gm. diarios. Sin embargo, es probable que la dosis óptima de oxitetraciclina quede entre unos 2 y 5 gm. diarios.

La oxitetraciclina diariamente en combinación con la estreptomicina intermitentemente representa un régimen farmacológico aceptable y útil en el tratamiento de la tuberculosis pulmonar activa.

RESUME

Oxytétracycline (Terramycine) quotidienne et Streptomycine intermittente dans le traitement de la tuberculose pulmonaire: Une investigation sur l'administration quotidienne de deux grammes d'Oxytétracycline

Vingt malades atteints de tuberculose pulmonaire en activité ont été choisis pour recevoir un traitement de 120 jours à la dose de 2 grammes d'Terramycine orale par jour et 2 grammes de streptomycine intra-musculaire tous les trois jours.

L'amélioration, du point de vue clinique et radiologique, était étroitement parallèle à celle d'un traitement intermittent par la streptomycine et par l'oxytétracycline à la dose de 5 grammes par jour; toutefois, elle était supérieure à celle qui était observée avec la streptomycine seule, administrée tous les trois jours.

Les réactions nocives à la dose quotidienne de 2 grammes étaient plus faibles, moins persistantes et moins fréquentes qu'avec la dose d'oxytètracycline de 5 grammes par jour.

Les modifications de la flore microscopique des fèces et des crachats ont été étudiées. Les auteurs ont tenté d'établir une corrélation entre ces résultats et la toxicité sur le plan clinique.

Cette posologie de l'oxytétracycline n'a pas permis de prévenir complètement l'apparition de bacilles tuberculeux streptomycino-résistants. Ce mode d'administration s'est montré supérieur à celui de la streptomycine seule à la dose de 1 à 2 grammes tous les trois jours.

Il semble que, lorsque l'oxytétracycline est associée à la streptomycine dans le traitement de la tuberculose pulmonaire, la dose quotidienne de 5 grammes d'oxytétracycline soit supérieure à la dose quotidienne de 2 grammes. Il est probable toutefois que la dose optima d'oxytétracycline se situe entre 2 et 5 grammes par jour.

L'administration quotidienne d'oxytétracycline, associée à un traitement intermittent par la streptomycine, est un mode de traitement satisfaisant et utile dans le traitement de la tuberculose pulmonaire en activité.

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STREPTOMYCIN AND OXYTETRACYCLINE (TERRAMYCIN) IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

Oxytetracycline (Terramycin) has been shown to have a bacteriostatic effect upon *M. tuberculosis* (1–4), but the drug has very little therapeutic effect in the treatment of tuberculosis when used as the sole chemotherapeutic agent (5). When oxytetracycline and streptomycin were used together, the emergence of streptomycin-resistant tubercle bacilli was markedly delayed or prevented (5, 6).

Miller and associates (6) have reported on 70 patients with pulmonary tuberculosis who were treated at Fitzsimons Army Hospital for 120 days with 5 gm. of oxytetracycline daily and 2 gm. of streptomycin every third day. The present study deals with 81 patients who received the two drugs.

PLAN OF INVESTIGATION

Oxytetracycline and streptomycin were administered in the following combinations:

> Seventeen patients received oxytetracycline (Terramycin[4]), 5 gm. daily by mouth, and streptomycin, 1 gm. twice weekly intramuscularly; 34 patients received oxytetracycline 1 gm. daily, and streptomycin, 1 gm. twice weekly; and 30 patients received oxytetracycline, 1 gm. daily, and streptomycin, 2 gm. one day a week.

As the results were similar in the three individual groups, the results are reported for the groups as a whole.

The primary purpose of the present study was to determine the effect of oxytetracycline upon the emergence of streptomycin-resistant tubercle bacilli. All of the patients had streptomycin-susceptible bacilli at the start of treatment. Primary sputum or gastric cultures were made on Herrold's egg-yolk medium with 0.02 per cent malachite green; the bacilli were suspended in distilled water and added to control and streptomycin-containing tubes. Susceptibility tests were performed on the same medium, containing 0, 10, and 100 γ of streptomycin per ml. Resistance to streptomycin has arbitrarily been defined as profuse growth (4 plus) on the 10 γ tube, equal to that on the control tube (6). Oxytetracycline-susceptibility tests were also performed on cultures from the first 20 patients in the series. The strains were obtained by being subcultured from primary growth on the solid medium to Dubos liquid medium with added albumin. The serial dilutions of oxyte-

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[2] A preliminary report on a portion of this material was presented before the joint Veterans Administration, Army, Navy Conference on the Chemotherapy of Tuberculosis in Atlanta, Georgia, February 10, 1953.

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[4] The Terramycin used in this study was contributed by Chas. Pfizer & Co., Inc., Brooklyn, New York.

tracycline were 100 γ, 50, 25, 12.5, and 6.25 γ. A culture tube containing no drug was also included. No definite level of growth can properly be called "resistant" in the case of oxytetracycline. Nevertheless, the concentrations of oxytetracycline in the blood rarely exceed 6 γ per ml. (7).

Selection of cases: The 17 patients who received 5 gm. of oxytetracycline daily were chosen specifically because of the fact that they had large cavities and sputum positive for *M. tuberculosis* which might be expected to remain positive for at least four months.

The 64 patients who received 1 gm. of oxytetracycline daily were chosen as consecutive patients who were in need of chemotherapy for pulmonary tuberculosis, with no other qualifying features except that no patient included in the report had had previous streptomycin therapy.

While in some instances oxytetracycline was continued beyond four months, the sputum findings and roentgenographic changes are reported at the end of four months of treatment. Most of the patients were continued on streptomycin, but para-aminosalicylic acid (PAS) was substituted for oxytetracycline at the end of the fourth month.

When a patient's sputum is reported as "negative," at least three twenty-four-hour sputum concentrates and three forty-eight-hour concentrates were negative for *M. tuberculosis* on microscopic and cultural examinations, as well as three gastric cultures. Patients who received streptomycin and oxytetracycline were treated in addition by bed rest and, when indicated, by pneumoperitoneum. No major surgery was performed, largely because excisional surgery is rarely performed in this division on patients who have received less than four months of chemotherapy.

RESULTS

One hundred and nine patients were started on oxytetracycline (Terramycin) and streptomycin treatment but four months of therapy were completed in only 81. The causes for discontinuation before the planned four months of treatment had been completed are as follows:

Irregular discharge	19
Diarrhea	7
Rash	2

Drug-susceptibility studies: At the start of treatment, 72 patients had sputum positive for *M. tuberculosis*. At the end of four months, 47 of these were still discharging tubercle bacilli. Any positive finding was reported as "positive," even if only one culture or smear of fifteen examinations showed tubercle bacilli. The presence of *M. tuberculosis* in the sputum of 81 patients who were started on streptomycin-oxytetracycline and completed four months of therapy was as follows:

	Absent	*Present*
	(on Concentrate and Culture)	
At start	72	9
At 4 months	47	34

Of the 47 patients who were discharging tubercle bacilli at the end of four months, the bacilli could be isolated on culture in 45. Of these, one strain was resistant to streptomycin on the only culture available. Two other strains showed equivocal results in that one culture showed 4-plus growth in the 10 γ streptomycin tube, but streptomycin susceptibility to this concentration was indicated in 2 to 5 other tests on positive cultures from the same patients obtained at approximately the same time. If all of these patients are considered to have had "resistant" strains, then 7 per cent of the patients who were discharging tubercle bacilli at the end of four months had streptomycin-resistant strains, and 4 per cent of those patients who had been discharging bacilli at the start of treatment had resistant strains at the end of four months.

The results of 111 tests of oxytetracycline susceptibility showed slight growth at the start of treatment in 2 instances in tubes which contained 50 γ of drug. At the end of one, two, three, and four months, individual cultures grew out in the 6, 12, and 25 γ oxytetracycline tubes. There was no instance of very profuse growth equal to that in the control tube (4 plus) in any of these tubes, nor any consistent increase from month to month. Two tests showed slight growth in 100 γ of oxytetracycline, one at the end of three months and the other at the end of four months.

Roentgenographic studies: At the start of treatment, 39 patients had far advanced disease, 37 had moderately advanced disease, and 5 had minimal lesions. In 80 per cent of the group, some degree of roentgenographic improvement was noted during the four-month period of observation and, in approximately one-half of the group, the degree of improvement was moderate or marked.

Drug toxicity: The only evidences of toxicity to oxytetracycline consisted of gastrointestinal intolerance, usually diarrhea. In most instances, the diarrhea subsided after a few weeks of treatment. This occurred in some degree in approximately one-fifth of the patients and was more pronounced in the patients who received 5 gm. of oxytetracycline daily. Even with 1 gm. daily, a number of older men had appreciable diarrhea. No special studies were made of the bacterial flora of the stools. Seven of the original 109 patients had to stop taking oxytetracycline before the end of four months of treatment because of severe persistent diarrhea. All but one of these patients were able to tolerate PAS. No patient developed a sprue-like syndrome (8) or clinical evidence of superinfection with oxytetracycline-resistant staphylococci (9). No patient developed a clinically detectable fungus infection.

As mentioned previously, most of the patients were placed on streptomycin and PAS at the conclusion of four to eight months on the streptomycin-oxytetracycline regimen. Approximately one in ten found PAS so much more irritating to the gastrointestinal tract or so much more productive of anorexia than oxytetracycline that PAS could not be given. Patients who experienced this difficulty were treated with isoniazid or oxytetracycline.

Although 5 gm. daily of oxytetracycline is not, in the present writers' opinion, a practical dosage schedule from the standpoint of patient acceptance, 1 gm. daily in most instances was considered by the patients to be more acceptable than the usual daily dosage of PAS. In addition, marked anorexia and even weight

loss have been noted in 5 to 10 per cent of the patients on this service who receive PAS. When these patients were placed on oxytetracycline (although such patients are not included in this study), these symptoms usually disappeared.

DISCUSSION

The advent of isoniazid has materially altered the therapeutic approaches existing prior to its use. If the combination of streptomycin and isoniazid can be shown to be sufficiently effective as to therapeutic results and low toxicity, as well as free from the danger of drug resistance, such additional therapy as PAS or oxytetracycline (Terramycin) may no longer be needed. Nevertheless, at the present time streptomycin and PAS are still widely used, but PAS has certain features which may, in some cases, impair its usefulness. These are its unpleasant taste, associated gastrointestinal symptoms, and allergy characterized by rash, chills, and fever. For this reason a search for an acceptable substitute is in order.

When streptomycin is used alone in daily dosage, the high degree of emergence of streptomycin-resistant tubercle bacilli has been well documented. Dye (10), in analyzing 118 patients who were treated with 1 gm. of streptomycin twice weekly, without PAS, found that the strains of 35 per cent became resistant; when PAS was given daily in addition, 2 per cent of the patients who had been discharging bacilli at the start of treatment, or 5 per cent of those who discharged bacilli at the end of four months, had drug-resistant strains. Of 484 Veterans Administration patients treated with 1 gm. of streptomycin twice weekly and daily PAS, 6 per cent of the patients with cultures positive for tubercle bacilli at the end of four months of treatment had streptomycin-resistant strains (11). As far as could be determined, there are no figures available on the question of streptomycin resistance in patients who received 2 gm. of streptomycin once weekly without PAS. In as yet unpublished material, the present writers have found the same incidence of drug-resistant strains developing in two groups of patients who received either 1 gm. of streptomycin twice weekly or 2 gm. of streptomycin once weekly, both with daily PAS. The number of patients with streptomycin-resistant strains in the present streptomycin-oxytetracycline group (4 per cent of those positive at the start of treatment and 7 per cent of those with positive cultures at the end of four months) would indicate that oxytetracycline and PAS are about equally effective in preventing or delaying the emergence of streptomycin-resistant strains of tubercle bacilli.

The roentgenographic changes were about the same as in most reported chemotherapy series. Thus, in the Public Health Service studies (12) at the end of four months' treatment with three randomized regimens (streptomycin-PAS, streptomycin-isoniazid, and isoniazid), the percentages of total roentgenographic improvement were respectively 65, 68, and 66. In the present study, approximately 80 per cent showed some degree of improvement, while Miller and his associates (6) reported 96 per cent roentgenographic improvement with streptomycin and oxytetracycline (5 gm. daily). In the present study, moderate or marked roentgenographic improvement was observed in 40 per cent, while, in the Public Health Service study, improvement occurred in 32, 41, and 53 per cent of the patients who received one or another of the three randomized regimens.

In the Fitzsimons study, approximately one-half of the patients attained moderate or marked roentgenographic improvement.

Sputum "conversion" figures were lower in the present series (35 per cent) than in the Public Health Service study (58 per cent of those who had been "positive" at the start of treatment) or in the Fitzsimons study (77 per cent). The reason for the discrepancy with the Fitzsimons figures is not clear, although it will be recalled that the first seventeen (20 per cent) of our cases were deliberately chosen because of large cavities and the anticipation of positive cultures even at the conclusion of treatment. If these are excluded, the percentage of sputum conversions then becomes 50 per cent, or the same as the Public Health study results (12) with large groups on streptomycin-PAS or isoniazid.

SUMMARY

Oxytetracycline (Terramycin) and streptomycin were administered for a four-month period to 81 patients with pulmonary tuberculosis. Seventeen patients received 1 gm. of streptomycin twice weekly and 5 gm. of oxytetracycline daily, 34 were given 1 gm. of streptomycin twice weekly and 1 gm. of oxytetracycline daily, and 30 received 2 gm. of streptomycin once weekly and 1 gm. of oxytetracycline daily.

In the dosage of 1 gm. daily, oxytetracycline toxicity was insignificant and patient acceptance was superior to that for para-aminosalicyclic acid (PAS). Roentgenographic changes and sputum "conversion" values did not differ appreciably from those reported for streptomycin and PAS. Three patients showed streptomycin-resistant strains of tubercle bacilli at the end of the treatment period, and 42 had streptomycin-susceptible strains. These values (4 per cent of those "positive" at the start of treatment and 7 per cent of those "positive" at the end of treatment) are comparable to those obtained with similar regimens using PAS instead of oxytetracycline.

In patients requiring streptomycin therapy but showing evidence of PAS intolerance, toxicity, or allergy, oxytetracycline in a dosage of 1 gm. daily can be used as a substitute for PAS with no higher incidence of the emergence of streptomycin-resistant strains of tubercle bacilli.

SUMARIO

La Estreptomicina y l'Oxitetraciclina (Terramicina) en el Tratamiento de la Tuberculosis Pulmonar

A 81 tuberculosos pulmonares se les administraron oxitetraciclina (Terramicina) y estreptomicina durante un período de cuatro meses. Diecisiete recibieron 1 gm. de estreptomicina dos veces semanales y 5 mg. de oxitetraciclina diariamente, 34 recibieron 1 gm. de estreptomicina dos veces semanales y 1 gm. de oxitetraciclina diariamente y 30 recibieron 2 gm. de estreptomicina una vez a la semana y 1 gm. de oxitetraciclina diariamente.

Con la dosis de 1 gm. diario, la toxicidad de la oxitetraciclina fué insignificante y la tolerancia de los enfermos superior a la mostrada para el ácido para-aminosalicílico (PAS). Las alteraciones radiográficas y las cifras de viraje del esputo no discreparon mayor cosa de las comunicadas para la estreptomicina y el PAS. Tres enfermos revelaron al terminar el período de tratamiento cepas estreptomicinorresistentes del bacilo tuberculoso y 42 tenían cepas estreptomicinosensibles. Esas cifras (4 por ciento de los "positivos" al comenzar el tratamiento y 7 por ciento de los "positivos" al terminar el tratamiento) son comparables a las obtenidas con regímenes semejantes en que se usa el PAS en vez de oxitetraciclina.

En los enfermos que requieren estreptomicinoterapia pero que muestran signos de intolerancia, toxicidad o alergia hacia el PAS, cabe usar la oxitetraciclina a dosis diarias de 1 gm. como substituto del PAS sin mayor incidencia de la formación de cepas estreptomicinorresistentes del bacilo tuberculoso.

RESUME

Streptomycine et Oxytétracycline (Terramycine) dans la traitement de la tuberculose pulmonaire

L'oxytétracycline (Terramycine) et la streptomycine furent administrées chez 81 malades atteints de tuberculose pulmonaire pendant une période de quatre mois. Dix-sept malades recurent 1 g. de streptomycine deux fois par semaine et 5 g. d'oxytétracycline par jour, 34 recurent 1 g. de streptomycine deux fois par semaine et 1 g. d'oxytétracycline par jour, 30 recurent 2 g. de streptomycine une fois par semaine et 1 g. d'oxytétracycline par jour.

A la dose de 1 g. par jour, la toxicité de l'oxytétracycline était négligeable; la tolérance était supérieure à celle observée pour l'acide para-aminosalicylique (PAS). La proportion des modifications radiologiques et de la conversion des crachats ne différait pas de façon appréciable de celle rapportée pour la streptomycine et le PAS. A la fin de la période de traitement, des souches de bacilles tuberculeux streptomycino-résistantes étaient présentes chez 3 malades et des souches streptomycino-sensibles chez 42. Ces valeurs (crachats "positifs" 4% au début du traitement et crachats "positifs" 7% a la fin du traitement) sont comparables à celles obtenues avec le même programme de cure, le PAS remplaçant l'oxytétracycline.

Chez les malades justiciables de la streptomycinothérapie, mais présentant une intolérance au PAS, toxicité ou allergie, l'oxytétracycline a la dose de 1 g. par jour peut remplacer le PAS sans que la fréquence d'apparition de souches de BK streptomycinorésistantes s'élève.

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AN EVALUATION OF FACTORS AFFECTING THE ALVEOLAR-ARTERIAL OXYGEN TENSION GRADIENT IN CHRONIC PULMONARY DISEASE[1,2,3]

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INTRODUCTION

The alveolar-arterial oxygen tension gradient may be increased as a result of one or a combination of three major patho-physiological mechanisms: (*a*) normal perfusion of poorly ventilated alveoli, i.e., increased venous admixture; (*b*) decrease in total diffusing surface area of the alveolar-capillary membrane; and (*c*) impairment of diffusion of oxygen across the alveolar-capillary membrane. All of the three mechanisms have been considered in this study. Nevertheless, the primary attention has been directed to the impairment of diffusion of oxygen across the alveolar-capillary membrane and its resultant effect upon the alveolar-arterial oxygen tension gradient.

Pathologic and physiologic alterations of the alveolar-capillary membrane have been established in several relatively uncommon disorders of the lungs. These include acute interstitial fibrosis (1), chronic beryllium granulomatosis (2, 3), sarcoidosis (3, 4), acute miliary tuberculosis (5), scleroderma (3, 6), and lymphangitic carcinomatous metastasis (6) of the lungs. The anatomic alteration observed in these cases has been the presence of fibrous, granulomatous, or neoplastic invasion of the alveolar-capillary membrane. The physiologic counterpart has been an impairment of diffusion of oxygen across the membrane.

Since impairment of oxygen diffusion has been described in these less common pulmonary disorders, it does not seem improbable that similar disfunction might occur occasionally during the course of some of the more common lung diseases, particularly those in which fibrosis is a predominant feature.

However, a recent report failed to reveal evidence of impaired diffusion in patients with chronic pulmonary emphysema and fibrosis (7). Nevertheless, further observations regarding this problem seemed advisable.

METHODS AND MATERIAL

Thirty-two patients with chronic pulmonary diseases were studied. There were 9 patients with pulmonary emphysema, 5 each with silicosis and bronchiectasis, 7 with nonmiliary pulmonary tuberculosis, one with acute miliary tuberculosis, and 5 with diffuse pulmonary fibrosis of undetermined etiology.

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[2] Presented before the Medical Session, as part of the session of *Tuberculosis and Related Subjects*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 20, 1953.

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TABLE 1

MEASUREMENTS OF VENTILATION, BLOOD GASES, ALVEOLAR-ARTERIAL OXYGEN TENSION GRADIENT AND ITS COMPONENTS IN 32 PATIENTS WITH CHRONIC LUNG DISEASES

PATIENT	AGE	VITAL CAPACITY (cc.)	PER CENT OF VITAL CAPACITY IN 3 SECONDS (TIMED VITAL CAPACITY)	MAXIMUM BREATHING CAPACITY (PER CENT OF PREDICTED)	TOTAL LUNG VOLUME (cc.)	RESIDUAL AIR (PER CENT)	RESTING				VENOUS ADMIXTURE AS PER CENT OF CARDIAC OUTPUT	DIFFUSION COEFFICIENT DO_2
							Arterial Carbon Dioxide Content (Volume Per Cent)	Arterial Oxygen Saturation (Per Cent)	Effective Alveolar Oxygen Tension $P^E_{AO_2}$	Alveolar-Arterial Gradient (mm.)		
Average Normal Values												
		3,500	97	100	5,500	<35	42	94	80	<12	<6	>15
Emphysema												
FM	44	3,200	45	77	9,852	56	42.9	94.5	84.5	17.3	14	29
AH	48	2,900	59	40	8,063	57	52.7	86.8	69.7	21.4	29	13
AG*	52						54.8	85.0	75.8	27.6	30	9
GB	44	3,600	83	83	6,669	43	49.1	81.3	55.6	12.1	30	44
TL	62	1,600	59	20	6,002	67	53.6	80.2	61.2	16.0	18	11
AC	60	3,500	46	49	8,515	55	43.8	79.4	73.2	26.3	36	11
LC*	57	1,075	70				58.0	77.3	67.0	23.4	22	8
JL	41	3,800	82	57	7,725	41	44.1	74.8	65.8	13.4	18	18
AR*	59						52.3	64.6	55.0	14.8	22	12
Silicosis												
WM	48	3,200	91	91			38.9	93.4	93.8	26.5	22	9
GK	50	3,375	66	61	6,999	64	45.9	90.5	70.6	14.4	20	23
VS	46	3,300	85	63	6,478	46	44.6	87.9	79.2	23.2	25	11
AT	61	2,350	72	44	5,575	52	51.9	81.2	59.9	20.9	13	29
GH	54	1,100	64	23	6,435	61	48.4	78.5	85.4	40.9	27	4
Bronchiectasis												
CB	22	2,650	96	95	7,108	51	42.4	98.6	79.5	5.9	3	14
AC	59	1,700	91	93	5,011	60	40.5	95.5	83.0	23.1	21	9
OV	51	3,000	93	70	7,056	49	41.4	92.2	77.4	7.6	6	47
EO	38	2,700	96	64	5,685	46	43.2	92.2	81.3	19.5	18	11
JA	40	1,920	88	77	4,379	49	45.6	85.0	69.1	15.9	24	18
Tuberculosis (Chronic, Nonmiliary)												
MM	20	2,400	100	120	4,500	41	44.5	96.3	78.9	9.9	8	11
AA	42	4,100	85	108	8,118	38	41.3	93.9	77.4	17.4	19	24
TE	54	2,350	89	98	5,160	47	38.6	93.8	91.3	16.6	11	22
JM	18	3,000	87	78	4,839	34	42.7	92.3	81.9	20.4	20	19
PC†	62	2,400	92	42			34.1	90.2	84.8	13.5	11	9
MG	30	2,600	100	97	4,057	21	42.5	89.3	71.8	12.0	15	43
PH†	54	1,600	88	32			45.9	81.2	72.7	29.7	39	8
Acute Miliary Tuberculosis												
HS	43	3,200	88	145	5,382	30	21.7	96.8	106.4	20.4	9	8
Idiopathic Fibrosis												
AL	28	3,850	99	123	5,729	26	42.1	92.2	72.2	10.0	9	14
BE	51	2,300	100	63	5,590	59	44.5	87.1	73.7	23.0	16	12
JW	70	2,150	84	45	4,680	45	44.6	82.3	70.6	23.6	42	14
AQ	63	1,550	74	63	4,378	63	43.5	80.8	61.6	21.9	50	14
LG	60	1,080		70	3,659	63	58.4	44.0	59.8	30.0	51	8

* Severity of ventilatory insufficiency prevented completion of studies.

† Satisfactory lung volume studies not obtained.

The vital capacity and the per cent vital capacity performed in three seconds (timed vital capacity) were determined with the Gaensler-Collins vitalometer (8). Total lung volume and its subdivisions were determined by the method of Darling and associates (9). Oxygen content, oxygen capacity, and carbon dioxide content were determined by the Van Slyke-Neill manometric method (10). The partial pressures of oxygen and carbon dioxide in the arterial blood were determined by the direct technique of Riley, Proemmel, and Franke (11). The effective alveolar partial pressure of oxygen was calculated using the alveolar equation in the formula presented by Pappenheimer and associates (12). Thus, the alveolar-arterial oxygen tension gradient could then be determined. The two components of the A-a gradient, diffusion coefficient of oxygen and venous admixture percentage, were then determined using two levels of oxygenation in the manner outlined by Riley and associates (13).

TABLE 2

AVERAGE VALUES FOR EACH DISEASE OF DATA PRESENTED IN TABLE 1

DISEASE	NUMBER OF PATIENTS	VITAL CAPACITY (cc.)	PER CENT OF VITAL CAPACITY IN 3 SECONDS (TIMED VITAL CAPACITY)	MAXIMUM BREATHING CAPACITY (PER CENT OF PREDICTED NORMAL)	TOTAL LUNG VOLUME (cc.)	RESIDUAL AIR (PER CENT)	RESTING				VENOUS ADMIXTURE AS PER CENT OF CARDIAC OUTPUT	DIFFUSION COEFFICIENT DO_2
							Arterial Carbon Dioxide Content (Volume Per Cent)	Arterial Oxygen Saturation (Per Cent)	Effective Alveolar Oxygen Tension $p^e_{AO_2}$	Alveolar-Arterial Gradient (mm.)		
Average normal		3,500	97	100	5,500	35	42	94	80	12	6	15
Emphysema	9	2,810	63	58	7,804	53	50.1	80.4	67.5	19.1	24	17
Silicosis	5	2,665	76	58	6,372	56	45.9	86.3	77.8	25.2	21	15
Bronchiectasis	5	2,394	93	80	5,848	51	42.6	92.7	78.1	14.4	14	20
Tuberculosis	7	2,636	92	82	5,335	36	41.4	91.0	79.8	17.1	18	19
Acute miliary tuberculosis	1	3,200	88	145	5,382	30	21.7	96.8	106.4	20.4	9	8
Fibrosis	5	2,186	89	73	4,807	51	46.6	77.3	67.6	21.7	34	12

RESULTS

The compilation of results obtained in the individual cases is presented in table 1. The average values obtained for each disease are shown in table 2.

It is evident (table 1) that the residual air percentage was greater than the usually accepted normal value in all patients in whom lung volumes were measured. Increase in residual air *percentage* in some of the patients was in part secondary to decrease in total lung volume, the decreased total volume thereby causing a *relative* increase in the volume of residual air. It is thus evident that the use of residual air *percentage* alone is not a reliable means of classifying the severity, or even determining the presence, of emphysema. For this reason, the resting arterial oxygen saturation percentage was used in grading severity of emphysema, and the patients were listed in order of reduction in resting arterial oxygen saturation.

The average value obtained for the alveolar-arterial oxygen tension gradient

(A-a gradient) was increased in each disease (table 2). However, there were some persons in the present study whose A-a gradient was normal or only slightly increased (table 1).

The A-a gradient was greatest in those diseases characterized by diffuse pulmonary fibrosis, namely, silicosis and idiopathic pulmonary fibrosis. Venous admixture was uniformly increased, with few individual exceptions. The diffusion coefficient of oxygen across the alveolar-capillary membrane (DO_2) was significantly decreased in only a few instances (table 1).

DISCUSSION

In an effort to evaluate major factors which might affect the A-a gradient, ventilatory measurements were performed in addition to determinations of blood gas, venous admixture, and oxygen diffusion coefficient values. It seems justifiable, in considering the possible correlation of ventilatory measurements with the A-a gradient, to emphasize the concept of "external" ventilation, which refers to movement of air into and out of the tracheobronchial tree, and "internal" ventilation, which concerns the intrapulmonary distribution of inspired air, or alveolar ventilation.

Patients who had the most severe interference with external ventilation did not necessarily have any greater increase in A-a gradient than those with less impairment of external ventilation (table 1). The average values for ventilatory measurements and A-a gradient for the different diseases (table 2) reveal no real correlation between external ventilation and A-a gradient. There is, therefore, no significant correlation between impairment of external ventilation and the A-a gradient.

The average A-a gradient was increased in all diseases and was associated with increase in average venous admixture percentage (table 2). The increased alveolar-arterial oxygen tension gradient, therefore, would appear to be, in part, due to the continued perfusion of poorly ventilated alveoli.

Perfusion of poorly ventilated alveoli with resulting increase in venous admixture was not the only mechanism involved in these patients. The diffusion coefficient of oxygen in some instances was significantly reduced. Two patients (L. C. and A. G.) with severe emphysema had oxygen diffusion coefficients of 8 and 9, respectively. Donald and associates (7) and Richards (14) have pointed out that, in the presence of a reduced diffusion coefficient of oxygen, it is impossible to differentiate a reduction in total diffusing surface area from actual pathologic alteration of the alveolar-capillary membrane. The reduction in the diffusion coefficient of oxygen in the 2 patients with severe emphysema may, therefore, be due primarily to the marked reduction in total diffusing surface area. Thus, it is at present impossible to determine whether or not impairment of oxygen diffusion occurs in emphysema.

Patients with silicosis usually have attendant pulmonary emphysema. Pulmonary fibrosis usually predominates, however, and might possibly invade the alveolar-capillary membrane and impair diffusion of oxygen. Significant reduction in the diffusion coefficient of oxygen was observed in 2 patients with silicosis. One of these (W. M.) had only mild emphysema associated with considerable

diffuse fibrosis. Since there probably was not extensive reduction in diffusing surface area due to emphysema, it seems possible that there was fibrous involvement of the alveolar-capillary membrane with impairment of diffusion. Confirmation will require much further study of similar patients.

Bronchiectasis is usually a less diffuse disease with relatively little fibrosis; therefore, impaired diffusion of oxygen would not be expected. Impaired alveolar ventilation with resulting increased venous admixture probably is responsible for the increased A-a gradient observed. The one patient (A. C.) who had significant reduction in the diffusion coefficient of oxygen had severe bronchiectasis and contraction of the left lung. It was an almost functionless lung, and the other lung was markedly overdistended. There probably was severe reduction in diffusing surface area to account for the reduced diffusion coefficient.

Two patients (P. C. and P. H.) with tuberculosis had significant reduction in the diffusion coefficient of oxygen. Both had chronic bilateral pulmonary tuberculosis with considerable fibrosis. Neither would tolerate measurement of lung volumes, but there was no evidence of significant emphysema by either roentgenographic or physical examination. Therefore, impairment of diffusion might have been a reflection of the attendant fibrosis.

The one case of acute miliary tuberculosis had significant reduction in diffusion coefficient of oxygen with only slight increase in venous admixture. The increase in A-a gradient in this case may have been due to a diffusion barrier at the alveolar-capillary membrane. Impairment of diffusion in acute miliary tuberculosis with reversion toward normal as the inflammatory process responds to treatment has been reported (5). All such patients may not show complete recovery, since the inflammatory process might be replaced in part by fibrous tissue. Likewise, any patient with extensive pulmonary tuberculosis might also have residual fibrous alteration of the alveolar-capillary membrane with resulting impairment of diffusion of oxygen. Adequate study of many more patients will be necessary to clarify this.

The A-a gradient was above normal in all but one patient with idiopathic pulmonary fibrosis. The likelihood of impaired oxygen diffusion as a cause of the increased A-a gradient would appear to be greatest in this group for two reasons: the diffuse nature of the fibrosis; and the absence of significant emphysema, which minimizes the possibility of reduction in total diffusing surface area. Although the average diffusion coefficient was lower in this group than for any other disease (table 2), it was significantly decreased in only one case (L. G.) (table 1). Increased percentage of venous admixture, however, was an outstanding finding. It appears, therefore, that again impairment of diffusion is not the functional alteration primarily responsible for the increased A-a gradient. Instead, the increase in the A-a gradient is due primarily to continued perfusion of poorly ventilated alveoli.

SUMMARY

Ventilatory and blood gas studies were performed in 32 patients with chronic pulmonary disease.

The alveolar-arterial oxygen tension gradient was increased in nearly all cases.

No significant correlation between the ventilatory values and the A-a gradient was evident. The percentage of venous admixture was increased in all but 2 patients.

The diffusion coefficient of oxygen was significantly reduced in 9 patients. Impairment of diffusion, however, was most likely present in only the patient with acute miliary tuberculosis. The reduced diffusion coefficient in the remaining patients could be explained, for the most part, by reduction in diffusing surface area.

Thus, inadequate ventilation of normally perfused alveoli is apparently the primary cause for increase in the A-a gradient in these common lung diseases.

SUMARIO

Justipreciación de los Factores que Afectan la Pendiente de la Tensión del Oxígeno Alvéolo-Arterial en las Afecciones Pulmonares Crónicas

En 32 sujetos que tenían enfermedad pulmonar crónica, ejecutáronse estudios de la ventilación y de los gases sanguíneos.

En casi todos los casos, estaba aumentada la pendiente de la tensión del oxígeno alvéolo-arterial. No se notó ninguna correlación importante entre los valores de la ventilación y la pendiente A-a. En todos los enfermos, menos 2, había aumentado el porcentaje de mezcla venosa.

En 9 enfermos, estaba reducido significativamente el coeficiente de difusión de oxígeno, pero esta insuficiencia tenía más probabilidades de presentarse únicamente en los que padecían de granulia aguda. En los demás sujetos, cabía explicar, en su mayor parte, la disminución del coeficiente de difusión a base de la reducción del área superficial de difusión.

La inadecuada ventilación de los alvéolos normalmente perfundidos es, pues, aparentemente la causa primaria del aumento de la pendiente A-a en esas neumopatías corrientes.

RESUME

Une évaluation des facteurs influençant le gradient de la tension alvéolo-artérielle de l'oxygène dans la maladie pulmonaire chronique

L'étude de la ventilation et des gaz du sang à été effectuée chez 32 patients atteints d'affection chronique du poumon.

Le gradient de la tension alvéolo-artérielle de l'oxygène était augmentée dans tous les cas. Aucune corrélation significative entre les valeurs de la ventilation et le gradient alvéolo-artériel n'a été démontrée. Le taux de l'admixion veineuse était augmenté chez tous les malades sauf deux.

Le coefficient de diffusion de l'oxygène était réduit de façon significative chez 9 malades. Le plus souvent, l'altération de la diffusion n'était présente que chez le malade affecté de tuberculose miliaire aiguë. La réduction du coefficient de diffusion chez les autres malades du groupe pouvait en grande partie s'expliquer par la réduction de la surface de diffusion.

Ainsi, une ventilation insuffisante au niveau des alvéoles normalement irriguées semble être la cause initiale de l'élévation du gradient alvéolo-artériel dans ces affections ordinaires du poumon.

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THE PROGNOSIS OF SARCOIDOSIS[1,2]

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INTRODUCTION

A review of the literature reveals many conflicting statements concerning the prognosis in sarcoidosis. For example, Riley (1) studied a series of 52 patients who were followed for six months to nineteen years; he reported that 10 of these had died of sarcoidosis and 3 others of unrelated causes. Tuberculosis had developed in 6 of those who died and in 7 others. Only 17 had shown any evidence of improvement. Reisner (2) also found the prognosis in sarcoidosis to be poor. He studied 28 patients for one to fifteen years and found that 7 of them had died: 5 of tuberculosis, one of progressive sarcoidosis, and another of an undetermined cause. Six of the 7 patients who died had tuberculosis. In only 9 of the patients did the sarcoidosis regress significantly. Hunnicutt and his associates (3) had a similar experience. They observed 34 patients for varying periods up to eighty months and found that 5 of them had died: 2 of tuberculosis, one of sarcoidosis, and 2 of other causes. In addition, tuberculosis had developed in 3 others. Only 7 of them had shown any improvement.

In contrast, Garland (4) reported that, of 17 patients followed for six months to seven years, none died or developed tuberculosis and that in 10 of these the lesions regressed. King (5) observed similar results; none of his 37 patients died. In two months to four years, 26 of them improved and only 3 worsened. Ricker and Clark (6) sent questionnaires to 114 patients several years after a diagnosis of sarcoidosis had been made. Sixty-seven replies were received, and in all of these cases the patients were still alive. Hartweg (7), Stubbe (8), Cone (9), and Bruce and Wassén (10) also reported that the prognosis in sarcoidosis was good. Longcope and Freiman (11) reported on two series of cases in their outstanding monograph on sarcoidosis, one from the Massachusetts General Hospital and the other from the Johns Hopkins Hospital. In the Massachusetts General Hospital series, 37 patients were followed for two to more than twenty years, with only 2 deaths, one due to sarcoidosis and another due to an incidental neoplasm. In the Johns Hopkins Hospital series, 30 patients were followed for the same period of time, with 9 deaths; all were presumably due to sarcoidosis.

In spite of the fact that the present writers had no hope of settling this conflict, it did seem worth while to determine what had happened to those patients who had had a diagnosis of sarcoidosis made at the Mayo Clinic.

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[2] Presented before the Medical Session, as part of the session on *Nontuberculous Diseases of the Chest*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 19, 1953.

OBSERVATIONS

Only patients with a biopsy typical of sarcoidosis and without any other explanation for the disease were included in the present study. The records of such cases for the years 1940 through 1951 were reviewed. Follow-up information was obtained by subsequent examinations at the clinic and by follow-up letters.

The age and sex data for the 194 patients are given in table 1. Only 9 (4.6 per cent) of the patients with sarcoidosis were Negroes, but this is approximately ten times as great as the frequency of Negroes in the total patient population. One hundred and nineteen of the patients had a tuberculin test, the dose of PPD varying from 0.00002 to 0.005 mg. Twenty-three (19.3 per cent) of these patients

TABLE 1

SARCOIDOSIS: AGE AND SEX DISTRIBUTION OF 194 PATIENTS WITH SARCOIDOSIS

AGE	TOTAL		MALES		FEMALES	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
years						
0–9	1	0.5	1	1.3	0	—
10–19	8	4.1	4	5.3	4	3.4
20–29	34	17.5	15	19.7	19	16.1
30–39	56	28.9	22	29.0	34	28.9
40–49	37	19.1	15	19.7	22	18.6
50–59	42	21.6	12	15.8	30	25.4
60–69	12	6.2	5	6.6	7	5.9
70–79	4	2.1	2	2.6	2	1.7
Total	194	100.0	76	100.0	118	100.0
Mean	41.2 years		39.7 years		42.1 years	
Youngest	9 years		9 years		12 years	
Oldest	78 years		70 years		78 years	

had a positive reaction to the tuberculin. The Kveim test was not used in the present series. Bacteriologic studies of the biopsied tissue were made in 81 of the cases, without any positive findings. Some of the patients were given various combinations of the treatments available during the last fifteen years, including rest, roentgen therapy, vitamin D, and antimicrobial therapy, but there was no suggestion that any of these agents had affected the prognosis. In only a few of the most recent cases were cortisone and corticotropin given; so these drugs could not have had any effect on the survival rates given in this report.

The three-year and the five-year follow-up data are given in table 2 (12). It will be seen that 93 per cent of the patients in the three-year group were traced, and that 93.3 per cent of these traced patients were found to have survived for this period of time. Ninety per cent of the patients in the five-year group were traced, and 92.9 per cent of these patients traced for five years were alive at the

end of the five-year period. The apparent ambiguity which exists in the table between the three-year and five-year survival rates for the ages 30 to 49 and 50 or more years is due to the paucity and selection of data. An analysis of the data

TABLE 2

SARCOIDOSIS: SURVIVAL RATES BY AGE GROUP

AGE	PATIENTS		LIVED 3 OR MORE YEARS AFTER CLINIC DIAGNOSIS		PATIENTS		LIVED 5 OR MORE YEARS AFTER CLINIC DIAGNOSIS	
	Total	Traced	Number	Per Cent*	Total	Traced	Number	Per Cent*
years								
10–29	30	29	28	96.6	22	21	19	90.5
30–49	67	60	56	93.3	55	46	43	93.5
50+	47	45	41	91.1	32	31	29	93.5
Total....	144	134	125	93.3	109	98	91	92.9

* Based on traced patients. Inquiry as of January 1, 1953. Included in the three-year group are those patients who were diagnosed at the clinic three or more years prior to the time of inquiry, that is, 1949 or earlier; the five-year group includes those patients diagnosed in 1947 or earlier.

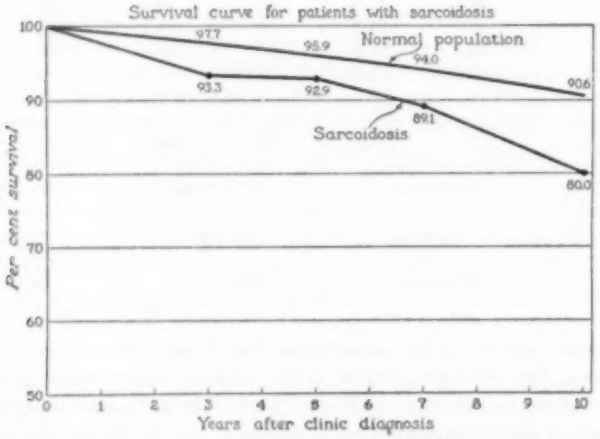

FIG. 1. The survival curve for patients who had sarcoidosis compared with the survival curve for a "normal" population of the same age and sex distribution.

revealed no evidence that the mortality rate was related to the age, sex, race, or tuberculin sensitivity of the patient.

The survival curve for patients who had sarcoidosis is given in figure 1, with supporting data in table 3. This is compared with a survival curve of a "normal" population of the same age and sex distribution. It may be seen that the patients with sarcoidosis have a slightly lower survival rate than the "normal" popula-

tion. Nevertheless, the five-year and ten-year survival rates are 96 per cent and 88 per cent, respectively, of the normal.

There was a total of 17 deaths in the entire group. Three of these were due to progressive sarcoidosis and one to miliary tuberculosis. Four patients died of a malignant neoplasm, one each of lupus erythematosus, rheumatic heart disease, biliary cirrhosis, and suicide. The cause of death was not determined in the remaining 5 cases.

Information concerning ability to work was obtained from 135 of the surviving patients. One hundred (74.1 per cent) reported that they were able to work full time, and an additional 17 (12.6 per cent) were able to work part time. Only 18 (13.3 per cent) were unable to work at all.

The incidence of tuberculosis in the patients who survived would have been

TABLE 3

SARCOIDOSIS: SURVIVAL RATES

PERIOD	PATIENTS		LIVED BEYOND INDICATED PERIOD	
	Total	Traced	Number	Survival Rate, Per Cent*
years				
3	144	134	125	93.3
5	100	98	91	92.9
7	63	55	49	89.1
10	23	20	16	80.0

* Based on traced patients. Inquiry as of January 1, 1953. Included in the three-year group are those patients who were diagnosed at the clinic three or more years prior to the time of inquiry, that is, 1949 or earlier; the five-year group includes those patients diagnosed in 1947 or earlier, and so forth.

of interest but could not be determined from the data available. Neither was it possible to obtain any significant data concerning the number of patients whose lesions had partially or completely resolved.

COMMENT

The present results seem to agree with those mentioned in the introduction indicating that the prognosis in sarcoidosis is good. On the other hand, those reports that the prognosis in sarcoidosis is poor are reliable and cannot be ignored. A careful review of all of these reports and comparison with the present data revealed no explanation for the discrepancy. It did not seem to be due to the age, sex, race, or economic status of the patient. Neither was there any evidence that the prognosis was related to the clinical manifestation of the disease or to the treatment which was given. The varying incidence of the subsequent development of tuberculosis in the reports cited is also puzzling. The answer to this puzzle may be the key to the larger problem of the prognosis, although the high mortality in the Johns Hopkins Hospital series was apparently due to progressive sarcoidosis and not tuberculosis. Riley (1) has suggested that the practice of

hospitalizing patients who have sarcoidosis in the same wards with tuberculous patients might account for the subsequent development of tuberculosis in many of these patients. However, he did not consider that these data warranted such a conclusion. His suggestion that this aspect of the problem be studied further is a good one and such a study is urgently needed. In the meantime it would seem unwise to expose a patient who has sarcoidosis to tuberculosis, and these patients should be urged to take extra precautions to avoid tuberculous infection.

Another possibility which must be considered is that sarcoidosis may not be a specific disease entity. It may be a group of diseases with certain similarities. If this is so, the various reports on sarcoidosis may not refer to comparable cases. When the etiology of sarcoidosis is discovered, it may be possible to diagnose the disease more specifically. Then it should be possible to determine its prognosis more accurately and also to answer some of the other puzzling questions about this disease.

SUMMARY

A review of the literature revealed conflicting reports concerning the prognosis in sarcoidosis. A follow-up study was made of 194 patients with sarcoidosis examined at the Mayo Clinic during the years 1940 through 1951. More than 90 per cent of the patients were traced, and the five-year and ten-year survival rates were found to be 92.9 per cent and 80 per cent, respectively. There was no evidence that the prognosis was influenced by age, sex, race, tuberculin sensitivity of the patient, or the treatment administered. Three of the deaths were due to progressive sarcoidosis and one to tuberculosis; 13 other patients died of unrelated or unknown causes. Although the variation in death rates in the various reports remains unexplained, it is suggested that exposure to tuberculosis with subsequent development of progressive tuberculosis may be a significant factor. Therefore, it is also suggested that patients who have sarcoidosis should avoid contact with tuberculosis.

SUMARIO

El Pronóstico en la Sarcoidosis

Un repaso de la literatura reveló datos contradictorios en cuanto al pronóstico en la sarcoidosis. En 194 enfermos de sarcoidosis examinados en la Clínica Mayo durante los años 1940 a 1951, inclusive, ejecutóse un estudio subsiguiente. Descubrióse el paradero de más de 90 por ciento de los pacientes y los coeficientes de sobrevivencia de cinco años y diez años resultaron ser de 92.9 y 80 por ciento, respectivamente. No hubo prueba alguna de que el pronóstico fuera afectado por la edad, el sexo, la raza, la sensibilidad a la tuberculina o el tratamiento administrado. Tres de las muertes se debieron a sarcoidosis progresiva y una a tuberculosis, falleciendo otros 13 enfermos de causas inconexas o desconocidas. Aunque permanece sin explicación la variación en la mortalidad que muestran las distintas comunicaciones, apúntase que la exposición a la tuberculosis con la subsiguiente aparición de tuberculosis evolutiva puede constituir un factor importante, por lo cual se sugiere que los enfermos de sarcoidosis eviten todo contacto con los tuberculosos.

RESUME

Le pronostic dans la sarcoïdose

Une analyse de la littérature a révélé des rapports contradictoires quant au pronostic de la sarcoïdose. Une étude portant sur cent quatre-vingt-quatorze malades atteints de sarcoïdose, examinés à la Clinique Mayo entre 1940 et 1951, inclusivement, a été entreprise. Plus de 90% des patients furent suivis et les taux de survie de cinq ans et de dix ans ont été respectivement 92,9 pour cent et 80 pour cent. L'influence sur le pronostic soit de l'âge, du sexe, de la race, de la sensibilité à la tuberculine ou du traitement effectué n'a pu être démontrée. Trois décès ont été causés par la sarcoïdose progressive et un par la tuberculose, 13 autres malades ont succombé à des affections différentes ou indéterminées. Bien que la variabilité des taux de mortalité des divers rapports demeure inexpliquée, les auteurs sont d'avis que l'exposition à la tuberculose avec développement ultérieur d'une tuberculose évolutive pourrait constituer un facteur significatif. En conséquence, il est également suggéré que les malades atteints de sarcoïdose évitent tout contact avec la tuberculose.

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ULCERATION OF THE BRONCHIAL STUMP AFTER RESECTION FOR TUBERCULOSIS[1,2]

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INTRODUCTION

Ulceration of the bronchial stump presumed to be tuberculous has been recognized since pulmonary resection became an accepted method of treatment for tuberculosis. Overholt and Wilson (1) reported this complication in 4 of 19 cases in which resection was performed in the presence of tuberculous bronchitis. Other reports (2–14) in the English literature have cited incidences below 12 per cent.

At Firland Sanatorium, the frequency of ulceration in the bronchial stump seemed greater than that reported in any other series. The first 400 resections done on 389 patients at this institution were reviewed in an effort to evaluate the problem. All were performed between June 1946, and August, 1951, at a time when long-term antituberculous chemotherapy was not being used. Each consisted of removal of a complete bronchopulmonary segment or more. Final data were collected one year or more after the last resection.

OBSERVATIONS

One hundred and sixty-one of the 400 resections were followed by bronchoscopic examinations after the surgical period, 142 primarily because of the presence of sputum positive for tubercle bacilli and 19 for other reasons in patients with sputum negative for tubercle bacilli. Ulceration of the bronchial stump was found in 93 of the former group and in 4 of the latter. While the presence of this complication had no known influence on mortality, it was frequently considered a source of sputum positive for tubercle bacilli and, in one case, of troublesome hemoptysis. The ulceration was indistinguishable from tuberculous endobronchitis seen elsewhere in the tracheobronchial tree and, in each instance, was diagnosed by the bronchoscopist as a tuberculous lesion. These findings are summarized in table 1.

In 64 of 93 patients with "positive" sputum, the only recognized source of tubercle bacilli was ulceration of the bronchial stump. Three patients could not be followed until healing occurred; another died, and a tuberculous ulcer was found in the bronchial stump at post-mortem examination. Three failed to "convert" their sputum with healing of the ulcers; the remaining 57 "converted."

Twenty-nine of the 93 patients with bronchial stump ulcers were considered to have additional sources of sputum positive for tubercle bacilli. Eleven of these

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[2] Presented before the Medical Session, as part of the session on *Surgery in the Treatment of Pulmonary Diseases*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 21, 1953.

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had second operations; in 4, the stump ulcers were still unhealed and active tuberculous bronchitis was demonstrated upon pathologic examination. The remaining 18 failed to attain "negative" sputum after healing of the ulcers.

Fourteen of the patients died during the first postoperative week. The remaining 386 resections were analyzed statistically in an effort to determine what factors might have contributed to the occurrence of the ulceration. The factors studied were tested individually by the chi-square method. A chi-square with P equaling 0.05 was considered significant, 0.01 highly significant. To avoid errors due to cross correlation, those factors which alone appeared significant, or nearly so, were broken down into subgroups so that it was possible to test by chi-square for the effects of one factor with one, two, or more of the other factors held constant.

TABLE 1

ULCERATION OF THE BRONCHIAL STUMP

400 Consecutive Resections

	CASES	ULCERS	PER CENT
Pneumonectomies	164	36	23.38
Lobectomies and/or segmental resection	246	61	24.80
Totals	400	97	24.25

Thereafter the ulcers were studied to determine significant points about their behavior.

Analysis of Factors

Factors of no significance: There was no correlation between the occurrence of bronchial stump ulceration and the age, race, and sex of the patient; nor was there correlation with the stage and duration of the parenchymal tuberculosis or the extent of the resection.

The other factors studied are considered individually and in more detail.

Antituberculous drugs: Only 3 of the resections were done prior to the use of streptomycin, although 10 were without the protection of antituberculous drugs. Streptomycin or dihydrostreptomycin, with or without para-aminosalicylic acid, was used with surgery. The susceptibility of the patients' tubercle bacilli at the time of surgery was known in only 39 instances. Thus, it was necessary to compare the various drug regimens to arrive at any valid conclusions.

Many regimens of drugs were used before, during, and after the surgical period. By use of the Veterans Administration statistics on the emergence of strains of tubercle bacilli resistant to streptomycin (15), it was possible to assign each of the 386 cases to one of the following groups:

Group A: Patients who prior to surgery had received courses of drugs which probably resulted in 20 per cent or more having streptomycin-resistant organisms, and who received three to six weeks of drugs with surgery

Group B: Patients who received no drugs prior to the surgical period or who received less than the above amounts, and who also were given drugs for three to six weeks with surgery

Group C: Patients who had their only drug therapy during the surgical period and who received such therapy for longer than six weeks

Group D: Patients who received no drugs

As may be seen in table 2, the drug regimens constituted a highly significant factor in the occurrence of bronchial stump ulcer ($P < 0.01$). Regimen *A* was inferior to *B* in preventing the complication ($P < 0.01$). The findings suggested, but did not establish, that regimen *C* was the most effective in avoidance of ulcers. No conclusions could be drawn regarding regimen *D* because of the small number of cases.

TABLE 2

DRUG REGIMENS

	GROUP A DRUGS RECEIVED BEFORE AND 3 TO 6 WEEKS DURING SURGERY	GROUP B NO DRUGS RECEIVED PRIOR TO SURGERY; DRUGS GIVEN 3 TO 6 WEEKS DURING SURGERY	GROUP C DRUGS GIVEN ONLY DURING SURGERY AND FOR LONGER THAN 6 WEEKS	GROUP D NO DRUG THERAPY
Total cases	112	225	39	10
Ulcers	41	46	7	3
Per cent	36.61	20.44	17.95	30.00

TABLE 3

PREOPERATIVE BRONCHOSCOPIC FINDINGS

	NORMAL	KNOWN TUBERCULOUS BRONCHITIS OR FIBROSTENOSIS	NONSPECIFIC INFLAMMATION
Total cases	206	96	63
Ulcers	51	23	22
Per cent	24.76	23.96	34.92

Preoperative bronchoscopic findings: Twenty-one of the 386 patients did not have bronchoscopic examinations, and one ulcer occurred in this group. In the remaining 365 patients, the preoperative bronchoscopic appearance of the bronchi to be amputated could be grouped into three categories (normal, known tuberculous bronchitis or fibrostenosis, and nonspecific inflammation) as shown in table 3.

In the second category (known tuberculous bronchitis or fibrostenosis), 2 patients were known to have active tuberculous bronchitis at the time of operation and both developed ulcers of the stumps. The remaining ones had previously exhibited tuberculous endobronchitis which was inactive at the time of surgery or had fibrostenosis which may have been due to an earlier tuberculous bronchitis. The third group had findings which were described by the bronchoscopists as

"nonspecific inflammation"; that is, erythema and edema of the bronchial mucosa without ulceration, granulations, or mucosal tubercles.

Testing the factor of preoperative bronchoscopic findings alone did not reveal any significant difference in the incidence of ulcers in the three categories ($P > 0.05$). But when the testing was carried further by holding drug regimens and type of parenchymal tuberculosis constant a significance was revealed ($P < 0.05$). The presence of preoperative nonspecific inflammation in the bronchus was a significant factor in the postoperative occurrence of stump ulceration.

Type of parenchymal tuberculosis: The type of parenchymal tuberculosis by roentgenographic interpretation existing at the time of operation and its correlation with the occurrence of ulceration of the bronchial stump is shown in table 4.

The observed higher incidence of ulcers when the resections were done in the presence of exudative parenchymal tuberculosis was not significant when tested alone or with drug regimens, and preoperative bronchoscopic findings held constant ($P > 0.05$).

TABLE 4

TYPE OF PARENCHYMAL TUBERCULOSIS

	PRODUCTIVE	MIXED	EXUDATIVE
Total cases	116	185	85
Ulcers	22	47	28
Per cent	18.97	25.41	32.94

Preoperative bacteriologic sputum status: In this series of resections, only 29 were done in the presence of known "negative" sputum cultures, now one of the widely accepted criteria for localized resections. Five of these patients (17.24 per cent) developed stump ulcers. Three hundred and fifty-seven cases had "positive" sputum or cultures had not been done preoperatively. Of these, 92 (25.77 per cent) developed stump ulcers ($P > 0.05$).

Method of bronchial closure: Although various materials such as steel wire (16, 17), tantalum wire (18), and nylon (19) have been recommended for bronchial closure, all of these bronchi were closed with fine black silk. It has been suggested that ulcers tend to occur in the bronchial stumps at the site of mattress sutures (1, 6). Of 203 cases with bronchial closure using mattress sutures, ulceration occurred in 38 (18.7 per cent). Of the 183 patients in whom no mattress sutures were left in the stumps, 59 (32.2 per cent) developed ulcers. There appeared to be a significantly higher incidence of ulcers when mattress sutures were not used ($P < 0.01$). But when subgroups were tested, holding drug regimens and preoperative bronchoscopic findings constant, P was greater than 0.05. Thus, the apparent significance regarding the two types of sutures was due to an error incident to cross-correlation of other factors.

Pathological examination of resected specimens: One hundred and eighty-one surgical specimens were examined grossly and microscopically for evidence of

tuberculous endobronchitis. Seventy of those were from patients who subsequently developed stump ulcers, thus weighting the data toward that group. For that reason it was not possible to set up any correlation which appeared statistically valid.

By examination of the specimens from the 70 patients who later had ulceration of the bronchial stump, it was established that 39 had peripheral bronchitis but none in the amputated bronchus; 21 had active tuberculosis in the amputated as well as in the peripheral bronchi; 5 had no demonstrable tuberculosis in any bronchus. This suggests that the presence of peripheral tuberculous bronchitis correlated more closely with the development of the ulceration of the stump than did bronchitis found at or near the site of amputation of the bronchus.

Study of the Ulcers

Diagnosis and time of occurrence: All of the ulcers were diagnosed by inspection at bronchoscopic examinations done for some specific indication, usually the persistence of tubercle bacilli in the sputum. Fifty-five ulcers were noted to occur within the first six months after operation; 33 were first seen between six and twelve months; and 9, after one year. One was diagnosed twenty-one months after operation.

Suture material in the stumps: In 71 of the stumps, suture material projected through the bronchial mucosa at the time the ulcers were being observed and treated. In 31, the ulcerations did not heal until after the sutures were expectorated, removed, or became covered by bronchial mucosa. There was, however, apparent healing of the ulcers in the remaining cases followed while sutures were still visible.

Treatment and healing of ulcers: The majority of the ulcers were observed at a time when it appeared necessary to reserve the use of antituberculous drugs for more life-threatening situations. Only 9 were treated primarily with streptomycin, with or without para-aminosalicylic acid. The rest were treated by application of 30 per cent silver nitrate directly to the ulcers and removal of suture material when possible. If healing was delayed, antituberculous therapy, including Tibione in 20 cases, was added. The benefits from Tibione were equivocal. Because so few of the ulcers were treated with streptomycin, with or without para-aminosalicylic acid, it cannot be said from this study that the use of these drugs is superior to local cautery. Nevertheless, it is believed from later experience that such is true.

As has been noted, the progress of the ulcers could not be followed in 4 cases, and 4 other patients had second operations while the stump ulcers were still active. All of the remaining ulcers were thought to have healed satisfactorily. Fifty-seven healed within four months; twenty-eight more were healed by the end of nine months, and the remaining 4 persisted for longer than nine months. The longest duration of any ulcer was eleven and one-half months.

The details on reversal of infectiousness with the healing of the ulcers have been given.

DISCUSSION

No biopsies of the ulcerated areas were taken, but it is believed that the majority, if not all, were tuberculous. Their appearance at bronchoscopic examination strongly suggested tuberculous lesions. Fifty-seven of 60 patients followed, who were discharging tubercle bacilli in the sputum without recognizable sources other than the bronchial stumps, became noninfectious upon healing of the ulcers. Five stumps subsequently examined grossly and microscopically, 4 after further surgery and one at post-mortem examination, had active tuberculous bronchitis.

The reason the incidence of ulceration of the bronchial stump was so high at Firland Sanatorium is not completely clear. Perhaps it is noteworthy that the resections were done at a time when the ideal postoperative care was considered to be at least six months of bed rest with six more months of graduated ambulation. Those patients who followed such advice and remained in the hospital for the full year after operation had frequent sputum examinations by culture. All patients who were found to have tubercle bacilli in the sputum after resection had bronchoscopic examinations of their bronchial stumps unless contraindicated. This probably permitted recognition of many ulcers which might have been overlooked under a less detailed follow-up.

Subsequent to the present series, the experience with continuous prolonged use of preoperative and postoperative drug therapy prescribed with full knowledge of the drug-susceptibility of the tubercle bacilli suggests that stump ulceration may be a minor problem in the future. The increased use of localized resections during such drug therapy may minimize the problem even further.

SUMMARY

Ulceration of the bronchial stump considered to be tuberculous occurred in more than 24 per cent of 400 resections for pulmonary tuberculosis.

Upon statistical analysis it was found that a significantly higher incidence of stump ulceration occurred in the group of patients who probably had the highest incidence of strains of tubercle bacilli resistant to drugs at the time of surgery. There were also more ulcers in surgical patients who had nonspecific inflammatory lesions of the bronchi. The observed higher incidence in the patients with exudative parenchymal tuberculosis who had resections was not statistically significant.

The use of mattress sutures in bronchial closure did not predispose to stump ulceration. Suture material projected through the bronchial mucosa in 71 of the ulcerated stumps appeared to interfere with healing of the ulcers in only 31.

Fifty-five of the ulcers were diagnosed within six months after operation, but one was noted twenty-one months postoperatively.

Primary treatment of the ulcers in this series by the more effective antituberculous drugs was limited to too few cases to state that it was the most effective method of treatment.

All ulcers followed satisfactorily eventually healed, usually within four months, but one persisted for eleven and one-half months.

SUMARIO

Ulceración del Muñón Bronquial Después de la Resección por Tuberculosis

Hubo ulceración del muñón bronquial considerado como tuberculoso en más de 24 por ciento de 400 resecciones por pulmonar tuberculosis.

En el análisis estadístico, observóse que había una incidencia significativamente mayor de ulceración del muñón en el grupo de enfermos que tenia probablemente la incidencia más alta de microbios fármacorresistentes al ejecutarse la cirugía. Hubo también más úlceras en los enfermos quirúrgicos que tenían lesiones inflamatorias inespecificas de los bronquios. La incidencia mayor observada en los enfermos con tuberculosis parenquimatosa exudativa en quienes se hicieron resecciones no reveló importancia estadística.

El empleo de suturas de colchonero para el cierre bronquial no predispuso a la ulceración del muñón. La salida del material de sutura a través de la mucosa bronquial en 71 de los muñones ulcerados no pareció afectar la cicatrización de las úlceras más que en 31.

Cincuenta y cinco de las úlceras fueron diagnosticadas en término de seis meses de la operación, pero una fué observada a los veintiún meses.

El tratamiento primario de las úlceras en esta serie por las drogas antituberculosas más eficaces se limitó a insuficientes casos para poder afirmar que ése fué el método más eficaz de tratamiento.

Todas las úlceras atendidas satisfactoriamente cicatrizaron con el tiempo, por lo general dentro de cuatro meses, pero una persistió durante once meses y medio.

RESUME

Ulcération du moignon bronchique après résection pour tuberculose

Dans 400 résections une ulcération du moignon bronchique attribuée à la tuberculose est survenue dans plus de 24 pour cent des cas.

L'analyse statistique a démontré qu'une fréquence significativement plus élevée de l'ulcération du moignon s'est produite parmi les patients chez lesquels l'incidence de bacilles résistants aux drogues au moment de l'intervention était la plus élevée.

On observait un nombre d'ulcérations plus grand chez les sujets porteurs de lésions bronchiques inflammatoires non spécifiques. L'incidence plus élevée, observée chez les malades affectés de tuberculose exudative du parenchyme et qui avaient été soumis aux résections, n'avait pas de valeur statistique.

L'emploi de sutures en U (Matress sutures) pour l'oblitération bronchique ne prédisposait pas à l'ulcération du moignon. Dans 71 cas d'ulcération du moignon les fils de suture perforaient la muqueuse bronchique, ils n'ont paru prévenir la cicatrisation du moignon que dans 31 cas.

Le diagnostic de cinquante-cinq de ces ulcérations a été fait dans les six mois qui ont suivi l'intervention, mais un des cas a été observé vingt-et-un mois après celle-ci.

Dans ce groupe, le traitement initial des ulcérations par les préparations antituberculeuses les plus efficaces fut limité à un nombre trop restreint de cas pour affirmer que cette méthode de traitement est la plus efficace.

Tous les cas d'ulcération qui ont été suivis ont guéri à un certain moment, habituellement en quatre mois, sauf un cas qui a persisté pendant onze mois et demi.

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DETECTION OF SMALL NUMBERS OF TUBERCLE BACILLI IN TREATED SPECIMENS[1]

Comparison of Mice, Guinea Pigs, and Artificial Media

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INTRODUCTION

Previous studies in this laboratory showed that C57 black mice, inoculated intranasally, and guinea pigs, inoculated intramuscularly, were at least ten times more susceptible to small numbers of *Mycobacterium tuberculosis* H37Rv from dispersed cultures than either the modification of Löwenstein's medium used in this laboratory or oleic-acid–albumin agar (1). Furthermore, when kept on a reduced diet, these mice appeared to be as susceptible to threshold doses as were guinea pigs. Finally, whereas large doses of organisms produced typical lung lesions in the mouse within two weeks of inoculation, no matter how small the dose, three weeks appeared to be sufficient for the development of detectable lesions. Smears and sections of the lesions could be shown by fluorescence microscopy to contain numerous acid-fast bacilli in contrast to the small numbers usually present in guinea pig lesions (2). This and the possible saving of time and expense by employing mice suggested that an attempt be made to duplicate the results of the pure culture experiments at the diagnostic level.

At the same time, the writers were interested to examine under quantitative conditions the contention of Jensen and Bindslev (3) and of Bloch (4) that large numbers of tubercle bacilli are so injured in the human body and/or by the homogenization process that they lose their infectivity for guinea pigs, while still retaining their ability to grow on artificial media. If this were so, then the advantage of the inoculated animal over cultural procedures previously observed with untreated pure cultures might well be lost.

MATERIALS AND METHODS

Procedure with specimens: The specimens selected for the experiments consisted of sputum samples, urine, or fasting gastric contents submitted for routine diagnosis, except for one instance in which H37Rv culture was added to sterilized sputum. Unless the contrary is indicated in the text, homogenization and concentration were effected by adding an equal volume of trisodium phosphate solution (23 per cent $Na_3PO_4 \cdot 12H_2O$) to the specimen, which was kept at 37°C. overnight. After dilution with ten to fifteen volumes of saline, the specimen was centrifuged at 3,500 r.p.m. for thirty minutes and the sediment was taken up in 1 ml. of supernatant fluid. Following examination by fluorescence microscopy, the concentrate was divided into three equal portions for inoculation intramuscularly into a guinea pig, intranasally into 2 or 4 mice, and onto culture medium, respectively. The optimal dose volume for the mouse is 0.06 ml. so that in most cases the total volume

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[2] Supported by grants from the John Winter Research Fund.

administered to the mice was from one-third to two-thirds of the amount cultured or inoculated into guinea pigs. This is a discrepancy which will be discussed later.

Media: The writers' modification of Löwenstein's medium has been described previously (1). The Löwenstein-Jensen medium was prepared in accordance with the detailed account given by Holm and Lester (5). Counting techniques, the strains of animals used, their maintenance and methods of inoculation, the recognition of infection, and the risk of cross-infection in the animal house have been considered in detail elsewhere (1). Fluorescence microscopy alone was used for examining smears and sections (2). The mice were kept on a deficient diet from the date of infection.

The normal basal diet of these animals consists of the following: maize meal, 40 per cent; wheat meal, 18 per cent; bran, 15 per cent; meat meal, (63 per cent protein), 10 per cent; dried buttermilk, 10 per cent; linseed meal, 5 per cent; charcoal, 0.5 per cent; crude salt, 0.5 per cent; and bone flour, 1 per cent. A vitaminized oil is added immediately prior to feeding. The mixture is fed as a dry ration to all of the experimental animals, supplemented by green lucerne (alfalfa) or green oats, and nursing mothers are given a supplement of powdered whole milk. The reduced diet consists of a proprietary mixture known as "calf pellets," of which the exact composition is not known, but it is a cereal mixture with a large proportion of bran. Water is added.

It has been found that, although mice survive reasonably well on this reduced diet, guinea pigs lose weight rapidly and have been known to die from inanition in six to eight weeks.

OBSERVATIONS AND RESULTS

Qualitative Examinations

As a preliminary test of the regularity of the mouse response to specimens known to contain *M. tuberculosis* and of the limitations of diagnosis based on the examination of lung tubercles, 10 sputum specimens, positive for acid-fast bacilli by direct smear, were concentrated with trisodium phosphate. Each was inoculated into 2 mice intranasally, one guinea pig intramuscularly, and onto Löwenstein medium. One mouse of each pair was sacrificed at three weeks and the other held for twelve weeks unless it died earlier.

In every animal examined at three weeks, lesions were found, varying from a few tubercles to extensive consolidation of the lung tissue. Enormous numbers of acid-fast bacilli culturally typical of *Mycobacterium tuberculosis* were present in both direct smear and sections. At twelve weeks the pathologic picture had progressed to almost complete involvement of the lung tissue in those animals which survived, and the lesions still contained numerous acid-fast bacilli. This experiment showed that the mouse could readily be infected by trisodium phosphate concentrates of "smear-positive" sputum and also confirmed that three weeks were sufficient for the development of recognizable lesions.

To test the mouse in routine diagnosis, specimens specially selected as probable threshold cases, and therefore critical, were studied. One-third of the concentrate, consisting of 1 ml. of resuspended deposit from trisodium phosphate-treated urines, was set aside for mouse inoculation. The remaining two-thirds were divided equally for culture and guinea pig inoculation following the routine diagnostic procedure. The guinea pigs were killed at eight weeks, and the cultures were held for ten weeks before being discarded.

The 4 mice used for each experiment together received almost two-thirds of the available inoculum. At the beginning, 2 mice were killed at the fourteenth day and the others at the twenty-first day. It soon became evident, however, that there were insufficient viable bacilli in these specimens to produce gross changes at two weeks and, subsequently, the animals were all kept for three weeks. When macroscopic lesions were detected, cultures were made on Löwenstein medium and also onto blood agar to detect other pathogenic bacteria. The remainder of the lung was placed in 10 per cent formalin. After one to two hours, when the lung was partially fixed and therefore easily incised, a suitable tubercle was cut through and one half was crushed on a slide. The rest was held for section in the event the smear proved negative for acid-fast bacilli.

The results of this group were disappointing. Only 12 of 80 specimens examined during more than one year gave positive results by any method. Of these, 5 were positive for *M. tuberculosis* by culture, 7 by guinea pig inoculation, and 8 by mouse inoculation. One specimen positive for *M. tuberculosis* by culture was negative in both animals. The mouse test alone failed to detect 5 specimens "positive" by combined culture and guinea pig inoculation. However, it did detect 4 "positives" which were "negative" by these combined methods. It is considered that, with the small numbers of viable bacilli apparently present in the concentrated specimens, the observed differences between the two animals should be attributed to chance rather than to difference in species sensitivity.

The findings from the above experiments, involving a total of 90 specimens, appear in table 4.

Quantitative Examinations

The following experiments were designed to overcome the delay in obtaining significant numbers of specimens positive for *M. tuberculosis* by the routine examinations set out above and were conducted in parallel with them.

Mycobacterium tuberculosis H37Rv added to sterilized sputum: Known numbers of *Mycobacterium tuberculosis* H37Rv, grown for ten days in Tween[3] medium (1), were added to sterilized sputum and dispersed through the sputum by agitation for five seconds in a Waring Blendor. Then, after treatment with selected concentrating agents, tenfold serial dilutions were made in 0.1 per cent albumin water. An equal amount of each dilution was used for culture and for the inoculation of 2 mice and one guinea pig, the combined dose for the 2 mice equaling that for the guinea pig.

In the results, which are presented in table 1, animal inoculation shows an advantage over culture and, of course, over direct microscopic examination. The mouse test alone failed to detect one "positive," the guinea pig two "positives," and culture six "positives," although two of the latter may have been obscured by contaminants in the specimens concentrated with trisodium phosphate. The mouse test alone detected one specimen which was "negative" by combined culture and guinea pig inoculation.

[3] Tween 80 is the proprietary name for the polyoxyethylene derivative of Sorbitan monooleate, obtainable from the Atlas Powder Co., Wilmington, Delaware.

Sputum diluted after homogenization: A sample of tuberculous sputum was homogenized by five seconds' treatment in a Waring Blendor, and two 10 ml. samples were withdrawn for treatment respectively with sodium hydroxide and trisodium phos-

TABLE 1

THE DETECTION OF MYCOBACTERIUM TUBERCULOSIS H37Rv ADDED TO STERILIZED SPUTUM UNTREATED AND AFTER TREATMENT WITH DIFFERENT CONCENTRATING AGENTS

TREATMENT	DILUTION OF CONCENTRATE	RESULTS				
		Direct Smear	Culture 4 Weeks (Number of Colonies Per Dose)	Mice 3 Weeks	Guinea Pig 6 to 10 Weeks	Combined Result, All Methods
NaOH, 4%, 30 minutes at 37°C.	10^{-1}	+	45	+	+	+
	10^{-2}	−	4	+	+	+
	10^{-3}	−	0	−	−	−
	10^{-4}	−	0	−	−	−
$Na_3PO_4 \cdot 12H_2O$, 15%, 24 hours at 37°C.	10^{-1}	+	C	+	+	+
	10^{-2}	−	C	+	+	+
	10^{-3}	−	C	+	+	+
	10^{-4}	−	C	−	−	−
$Na_3PO_4 \cdot 12H_2O$, 23%, 24 hours at 37°C.	10^{-1}	+	63	+	+	+
	10^{-2}	−	6	+	−	+
	10^{-3}	−	0	−	+	+
	10^{-4}	−	0	+	−	+
	10^{-5}	−	0	−	−	−
Untreated (control)	10^{-1}	+	U	+	+	+
	10^{-2}	−	U	+	+	+
	10^{-3}	−	U	+	+	+
	10^{-4}	−	28	+	+	+
	10^{-5}	−	0	−	−	−
	10^{-6}	−	0	+	+	+
	10^{-7}	−	0	−	−	−
Totals	20	4	8	13	12	14

C = contaminated culture. U = colonies uncountable.

Concentrating agents in the strengths given above were mixed with an equal volume of sputum.

Presumptive viable numbers equal for culture, two mice, and one guinea pig in each series.

Each dilution is considered as equivalent to a separate "specimen" for comparison of the three methods.

phate. Tenfold dilutions of the treated specimens were made, each dilution again being regarded as a separate specimen. The same amount of each concentrate was used for inoculating Löwenstein medium, one guinea pig, and 2 mice; the combined dose for the 2 mice equaling that for the guinea pig. The mice were killed at three

weeks, the colonies were counted at four weeks, and the guinea pigs were examined at ten weeks to allow ample time for lesions to develop.

Once again the superiority of animals over culture is evident in table 2. In this experiment the mouse test alone failed to detect one "positive" specimen.

Sputum diluted before homogenization: This was virtually a repetition of *Experiment 2*, designed to confirm the trend of results, to overcome any errors which may have resulted from clumping of bacilli under treatment, and to approach more closely the doses which would be used in practice. It might be argued that the mouse is unsuitable for diagnostic use because of the relatively small dose of concentrate which can be tolerated by the intranasal route (0.06 ml.) compared with that tolerated by a guinea pig (1 to 2 ml.). In the routine examinations reported above, the total dose given to the mice used (2 or 4) was 0.12 to 0.24 ml., while the guinea pigs and culture received 0.33 ml. In this experiment, the same ratio was observed, but at the lower figure, as only 2 mice were used per "specimen." Therefore, the guinea pig and the culture received 2.75 times the total mouse dose or 5.5 times the individual mouse dose.

TABLE 2

THE DETECTION OF TUBERCLE BACILLI IN TUBERCULOUS SPUTUM SERIALLY DILUTED AFTER CONCENTRATION WITH NaOH OR $Na_3PO_4 \cdot 12H_2O$

TREATMENT	DILUTION ("SPECIMEN")	RESULTS				
		Direct Smear	Culture 4 Weeks (Number of Colonies per Dose)	Mice 3 Weeks (Number Positive for *M. Tuberculosis*)	Guinea Pig 10 Weeks	Combined Result, All Methods
NaOH, 4%, 1 hour at 37°C.	10^{-1}	++	Ca. 200	+ (2)	+	+
	10^{-2}	+	19	+ (2)	+	+
	10^{-3}	−	2	+ (2)	+	+
	10^{-4}	−	0	+ (1)	+	+
	10^{-5}	−	0	−	−	−
$Na_3PO_4 \cdot 12H_2O$, 23%, 18 hours at 37°C.	10^{-1}	+	Ca. 300	+ (2)	+	+
	10^{-2}	+	30	+ (2)	+	+
	10^{-3}	−	3	+ (2)	+	+
	10^{-4}	−	0	+ (2)	+	+
	10^{-5}	−	0	−	+	+
	10^{-6}	−	0	−	−	−
Totals.....	11	4	6	8	9	9

Sputum dilutions regarded as separate "specimens" for diagnosis.

Total mouse dose (2 mice) equivalent to that used for culture and for guinea pig inoculation.

After homogenizing the sputum mechanically, tenfold serial dilutions were made in albumin water, and several 5 ml. samples of each dilution were treated separately with an equal volume of 4 per cent sodium hydroxide for thirty minutes. It was then

neutralized, centrifuged, and the supernatant discarded except for the lower 1 ml., which was used in the above-mentioned manner.

The superiority of animal inoculation over cultural methods is again shown in table 3. Despite the smaller mouse dose in this experiment, the mouse compares more than favorably with the guinea pig, detecting all the "positive" specimens found in this group, including one which was "negative" by combined culture and guinea pig inoculation. It will be noted, however, that, except with the four larger doses, only one mouse in each pair inoculated developed

TABLE 3

DETECTION OF TUBERCLE BACILLI IN TUBERCULOUS SPUTUM SERIALLY DILUTED BEFORE TREATMENT WITH 4 PER CENT SODIUM HYDROXIDE

SPUTUM DILUTION	"SPECIMENS"	RESULTS				
		Direct Smear	Culture 4 Weeks (Number of Colonies Per Dose)	Mice 3 Weeks (Number Positive for *M. Tuberculosis*)	Guinea Pig 6 Weeks	Combined Methods
10^{-3}	a	+	40	+ (2)	+	+
	b	+	60	+ (2)	+	+
10^{-3}	c	−	11	+ (2)	+	+
	d	−	13	+ (2)	+	+
10^{-4}	e	−	0	+ (1)	+	+
	f	−	0	+ (1)	+	+
	g	−	0	+ (1)	+	+
	h	−	0	−	−	−
10^{-4}	i	−	0	+ (1)	−	+
	j	−	0	−	−	−
	k	−	0	−	−	−
	l	−	0	−	−	−
Totals	12	2	4	8	7	8

Samples a–l regarded as separate "specimens" for diagnosis.
Total mouse dose (2 mice) approximately one-third that given to guinea pig.

confirmable lung lesions indicating the random distribution of viable units in the diluted samples. The failure of Löwenstein medium to detect small numbers of organisms is clearly demonstrated here.

When considered collectively, the figures for the various methods merit consideration, especially in the light of the careful experiments of Jensen and Bindslev (3) and of Holm and Lester (5). The former workers, who based their findings on serially diluted sputum samples vigorously shaken with glass beads, compared Jensen's modification of Löwenstein's medium with guinea pigs inoculated by the intraperitoneal route. The latter team tested 20,090 routine specimens on the same medium and by combined subcutaneous and intra-

peritoneal inoculation of guinea pigs. Both groups of workers found artificial culture to be more sensitive than animal inoculation, although the position was reversed with bovine strains in the hands of Holm and Lester.

In table 4, a general comparison is attempted of all the present findings to determine the relative accuracy of the different methods.

As might be anticipated, direct smear was of value only when specimens had a large population of acid-fast bacilli. Compared with animal inoculation and cultivation, its efficiency was low (39 per cent). When "specimens" consisted

TABLE 4

COMPOSITE RESULTS OF EXPERIMENTS COMPARING DIRECT SMEAR, CULTURE, AND GUINEA PIG AND MOUSE INOCULATION FOR DETECTING SMALL NUMBERS OF TUBERCLE BACILLI AFTER CONCENTRATION OF SPECIMENS

NATURE OF TEST	NUMBER OF SPECIMENS EXAMINED	NUMBER POSITIVE BY					
		Direct Smear	Culture 4 Weeks	Mice 3 Weeks	Guinea Pig 6 to 10 Weeks	Combined Results	
						Animals	All Methods
Routine specimens (Na_3PO_4)	90	10	15	18	17	21	22
Diluted sputum (NaOH, Na_3PO_4)	23	6	10	16	16	16	16
Sputum and H37Rv (NaOH, Na_3PO_4)	20	4	8	13	12	14	14
Totals	133	20	33	47	45	51	52
Percentage positive	—	38.6	63.4	90.3	86.5	98	100

TABLE 5

COMPARISON OF LÖWENSTEIN-JENSEN AND MODIFIED LÖWENSTEIN MEDIA

INOCULUM	DILUTION COUNTED	AVERAGE NUMBER OF COLONIES (4 WEEKS)	
		Löwenstein-Jensen	Modified Löwenstein
Sputum (NaOH, 30 minutes)	10^{-2}	75	80
H37Rv (NaOH, 30 minutes)	10^{-4}	46	45
H37Rv, Untreated	10^{-4}	36	46

of serial dilutions of sputum, animal inoculation gave positive results at dilutions from tenfold to one thousandfold beyond the last "positive" smear. Cultural methods yielded only 63 per cent of the total positives and, in the whole series, they detected only one specimen which was missed by animal inoculation. Taken together, inoculated animals detected 98 per cent of all the "positive" specimens (mice, 90 per cent; and guinea pigs, 87 per cent).

It is difficult to suggest any explanation for the diametrically opposite results obtained in these experiments to those mentioned above. However, the findings have been remarkably constant and, apart from the possible influence of damage to bacterial cells produced by shaking with glass beads and the relatively high

nonspecific death rate in guinea pigs reported by Holm and Lester, the media appeared to be the only possible source of error.

Comparison of media: As a deficiency in the cultural methods employed by the writers would have invalidated the results obtained, specimens containing acid-fast bacilli were diluted and counted on Jensen's medium and on the modification of Löwenstein's medium used in this laboratory. The specimens consisted of three "positive" sputa and a 10-day Tween culture of H37Rv. A portion of the latter acted as an untreated control. The rest of this culture and the sputum samples were treated with 4 per cent sodium hydroxide for thirty minutes at 37°C. and neutralized. Serial dilutions were made for counting on the two media in quadruplicate. Colonies were counted after three, four, and six weeks at 37°C.

Two of the sputum concentrates were contaminated and, therefore, the results are confined to the two H37Rv "specimens" and one sputum. Reference to table 5 indicates that these two media are not significantly different in their ability to support the growth of small numbers of tubercle bacilli. Hence, the difference between the results of the writers and those of Jensen and Bindslev are not attributable to differences in the media used.

DISCUSSION

These attempts to duplicate at the diagnostic level the writers' previous demonstration of the superiority of mice and guinea pigs over cultural methods in detecting small numbers of tubercle bacilli have led to several interesting observations concerning the relative merits of the different methods. A quantitative comparison has been attempted using specimens which contained small numbers of viable bacilli so that, although the number of positive results is not large, the comparison is highly critical.

Only a proportion of the results refers to single routine clinical specimens, for, to avoid undue delay in accumulating the necessary evidence, serial dilutions of tuberculous sputum have been used to obtain a high proportion of "specimens" of the borderline type with which these studies are most closely concerned. This approach was made because it was believed that much of the available highly contradictory evidence, based, as it usually is, on clinical specimens of unknown bacterial content, is difficult to interpret.

In the first place, no evidence has been found to support the suggestion of Jensen and Bindslev (3) that large numbers of tubercle bacilli in sputum are selectively damaged in the human host to the extent that they may lose their infectivity for guinea pigs and yet be capable of growth on artificial media. In experiments to be reported later, it was found that the lethal action of any concentrating agent on tubercle bacilli is of the same order, regardless of whether the bacilli are obtained from sputum, where they would have been exposed to "selective damage" in the human host, or from cultures grown in artificial media, where any such influence would be inoperative. It is considered, therefore, that any damage which occurs to the organisms is either of a physical or chemical nature associated with homogenization, and the writers have failed to find

that such damage selectively favors cultural processes. On the contrary, it will be seen that, with one exception (NaOH in table 1), mice and/or guinea pigs developed tuberculous lesions at dilutions tenfold or occasionally one hundred-fold greater than those yielding a positive culture. Furthermore, there has been no indication that any of twenty-four separate strains of *M. tuberculosis* finally isolated from specimens in these experiments differed initially in virulence for animals from each other or from *strain H37Rv*. In other words, these observations have supported Lange's belief (6) in the extremely high infectivity of tubercle bacilli for guinea pigs.

The "not inconsiderable degree of natural resistance (of guinea pigs to tuberculosis) which naturally asserts itself preferably with regard to tubercle bacilli that have been most injured in the human organism," postulated by Jensen and Bindslev to explain their results, has not been apparent in the strain of guinea pigs used in these experiments. It should be noted in this respect, however, that no case of naturally occurring tuberculosis has been detected in this strain, at least during the past eight years. It may be regarded, therefore, as a fully susceptible population with neither inherent nor acquired resistance to tuberculosis.

The primary object of the present study was to determine the possibility of replacing the guinea pig in diagnosis with a highly susceptible strain of mice (C57 black) inoculated intranasally and held on a reduced diet. It is shown in table 4 that, under the conditions observed, the mouse is as susceptible to infection (90 per cent) as is the guinea pig (87 per cent). The observed differences between these two animals are not regular (tables 1 to 3) and are therefore considered to be referable to sampling effects in specimens containing very small numbers of tubercle bacilli rather than to difference in species susceptibility. This is also supported by the failure of one mouse in each of several pairs used (table 3) to develop infection when borderline specimens were inoculated.

The essential differences observed between the mouse and guinea pig are in the speed of development of recognizable tubercles and in the ease of detection of acid-fast bacilli in the mouse lung lesions. As previously reported with pure cultures, specimens containing more than a few hundred viable organisms cause the formation of extensive characteristic grayish gelatinous tubercles in the lung within three weeks. As the viable bacilli are decreased, the number of tubercles diminishes. In some cases, only one tubercle may be found. Their tuberculous nature is readily confirmed by direct smears of crushed lesions examined by fluorescence microscopy.

With only one specimen in the present series, and that a specimen negative for *M. tuberculosis* in cultural and guinea pig tests, did a direct smear of the incised mouse lesion fail to detect tubercle bacilli which were later detected in a section of the lung examined by fluorescence microscopy. This is one of the important advantages of the mouse over the guinea pig, for it is well known that the detection of tubercle bacilli in smears or sections in guinea pig lesions is not always a simple matter. This is especially so when minimal lesions are present.

One very real disadvantage of the C57 black mouse in diagnosis is evident, however. This is the tendency for nonspecific lesions to develop following the introduction of foreign material into the lower respiratory tract. The possibility has already been noted of latent *Pasteurella pneumotropica* infection lighting up in mice inoculated intranasally with pure cultures (1). The same problem arose in the early stages of these tests, so that it became necessary to plate onto blood agar each lung showing macroscopic lesions in order to detect the presence of this organism. The elimination of *P. pneumotropica* from the local mouse colony by chemotherapy has apparently been successfully accomplished (7), but nonspecific lesions, bacteriologically sterile and often closely resembling tuberculosis, have continued to appear. It is now clear that lesions of this type may occur in up to 50 per cent of mice inoculated with autoclaved sputum alone or with autoclaved sputum treated with sodium hydroxide, trisodium phosphate, or sulfuric acid. Whether they are due to mechanical injury or to an exacerbation of latent viral infection is not certain. To overcome this difficulty in practice, it is necessary to examine all macroscopically suspicious lesions by smear (and, if "negative," by section). Although some time may be wasted on "negative" specimens, the actual saving of time made possible by substituting the mouse for the guinea pig is considered to compensate amply for any additional work involved.

An apparent disadvantage of the mouse, namely, the small volume tolerated by intranasal inoculation compared with that which can be given to a guinea pig, does not appear to be very important in practice. Using on the average 2 mice to each guinea pig (table 3), the latter received two or three times as much concentrate as both mice together. If there is any difference in the results between the two species under these conditions, then the advantage lies with the mouse.

The minimal safe period required to establish the presence of tubercle bacilli in a specimen by guinea pig inoculation is approximately four weeks, when, following a very large dose of organisms, the animals may be killed by a tuberculin shock or be shown to be suffering from progressive tuberculosis at autopsy. The writers have found that, with very small doses, lesions are either undetectable in guinea pigs macroscopically or have not progressed beyond the original focus at four weeks and that tuberculin sensitivity is unreliable at this stage of infection. Therefore, it is not possible in such cases to arrive at a diagnosis within, at the earliest, six to eight weeks. Thus, it would seem that the mouse has a potential usefulness as a medium for rapid virulence tests, giving an answer in two weeks with large doses or in three weeks when smaller numbers of bacilli occur in the specimen.

It is suggested that 4 mice be inoculated and 2 sacrificed at two weeks (tuberculin testing is of no value). If these prove "negative," the remaining pair may be killed at three weeks with every expectation of positive results even if viable tubercle bacilli were present in very small numbers in the original specimen.

It is of interest to note the relative merits of the mouse test alone and the

combined results of culture and guinea pig inoculation. Figures from the above experiments are as follows:

Specimens positive for *M. tuberculosis* by culture and guinea pig: negative by mouse = 7.
Specimens positive for *M. tuberculosis* by mouse: negative by culture and guinea pig = 6.

In conclusion, although many laboratories tend to rely on cultures alone, it has been the writers' experience that animal inoculation is more sensitive than culture, especially when only small numbers of viable tubercle bacilli are present. Moreover, animal inoculation should always be performed on urines and gastric contents, as these frequently contain nonpathogenic acid-fast bacilli. Serious consideration should be given to this before accepting without reserve the statement of Holm and Lester (5) that expert cultural methods surpass all other means of demonstrating small numbers of tubercle bacilli in routine pathologic specimens.

SUMMARY

Quantitative experiments have shown that both C57 black mice, inoculated intranasally, and guinea pigs, inoculated intramuscularly, are more reliable than cultural methods for detecting small numbers of tubercle bacilli in clinical material containing minimal numbers of tubercle bacilli treated with NaOH or $Na_3PO_4 \cdot 12H_2O$. This confirms previous results with untreated pure cultures. With sputum which contains large numbers of bacilli, culture alone is adequate.

The possibility of replacing the guinea pig with the mouse as a diagnostic animal is discussed. The advantage of the mouse lies in economy, the speed of development of detectable lesions (two to three weeks), and the ease of bacteriologic confirmation. There is, however, a marked tendency to develop nonspecific lung lesions, which must be examined microscopically to exclude tuberculosis.

It is believed that the mouse may prove a useful animal for rapid virulence tests, especially for urines or fasting gastric contents (where culture contamination is high) and, despite the tendency to develop nonspecific lesions, for routine diagnosis.

SUMARIO

Descubrimiento de Pequeñas Cantidades de Bacilos Tuberculosos en Ejemplares Tratados: Comparación de los Ratones, los Cobayos y los Medios Artificiales

Experimentos cuantitativos han demostrado que tanto los ratones negros C57, inoculados intranasalmente, como los cobayos, inoculados intramuscularmente, resultan más dignos de confianza que las técnicas de cultivo para descubrir bacilos tuberculosos en ejemplares clínicos que contienen cantidades mínimas de dichos bacilos tratados con NaOH o $Na_3PO_4 \cdot 12H_2O$. Esto confirma los resultados obtenidos anteriormente con cultivos puros no tratados. En el esputo que contiene grandes cantidades de bacilos, el cultivo resulta adecuado por sí solo.

Discútese la posibilidad de usar el ratón en vez del cobayo como animal de diagnóstico. La ventaja del ratón estriba en ser más económico, más rápida la aparición de lesiones observables (dos a tres semanas) y ser más fácil la confirmación bacteriológica. Ese animal muestra, sin embargo, una tendencia notable a la producción de lesiones pulmonares inespecíficas, que tienen que ser estudiadas al microscopio para excluir la tuberculosis.

Parece que el ratón puede resultar ser un animal útil para rápidas pruebas de virulencia, sobre todo para ejemplares de orina o de contenido gástrico en ayunas (en los que la contaminación de los cultivos es elevada) y, a pesar de la tendencia a la aparición de lesiones inespecíficas, para el diagnóstico corriente.

RESUME

Détection de faibles quantités de bacilles tuberculeux dans les spécimens ayant subi un traitement: Etude comparative (souris, cobayes, milieux artificiels)

Des expériences quantitatives ont montré que l'inoculation, intra-nasale chez la souris et intramusculaire chez le cobaye, est plus sûre que les procédés de culture pour déceler de faibles quantités de bacilles de Koch dans les spécimens cliniques renfermant une quantité minimime de bacilles tuberculeux traités par NaOH ou par $Na_2PO_4 \cdot 12H_2O$. Ceci confirme les résultats précédents obtenus avec des cultures pures. Lorsqu'il s'agit de crachats renfermant une grande quantité de bacilles tuberculeux, la culture seule est suffisante.

La possibilité de remplacer le cobaye par la souris comme animal de diagnostic est examinée. L'utilisation de la souris offre l'avantage de l'économie, de la rapidité du développement de lésions décelables (deux à trois semaines) et de la facilité de la confirmation bactériologique. Il y a toutefois une tendance marquée au développement de lésions pulmonaires non spécifiques, qui réclament l'examen bactériologique pour exclure la tuberculose.

Les auteurs sont d'avis que la souris peut être un animal utile pour les tests rapides relatifs à la virulence, surtout pour l'urine ou les liquides de lavage gastrique (dont le degré de contamination est élevé), et également comme procédé habituel de diagnostic, malgré cette tendance au développement de lésions non spécifiques.

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ON THE QUANTITATIVE EVALUATION OF THE ACTIVITY OF ANTITUBERCULOUS DRUGS IN EXPERIMENTAL MOUSE TUBERCULOSIS[1]

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INTRODUCTION

Among the methods for *in vivo* evaluation of the activity of antituberculous drugs, the intravenous infection of mice is being used more and more (1–4). This method is preferred because of the rapidity of its results and because it allows fairly good accuracy, especially when different drugs have to be compared, by reason of the relatively large number of animals which can be used.

The evaluation of results is usually made by three procedures (5): calculation of the mean survival time (T_{50}), estimation of the lung lesions, and variations in the weight curve.

The T_{50} determination has the advantage of being based on absolutely objective data, such as the mortality percentage on the different days which is easily calculated. Quantitative appraisal of variations in the weight curve is more difficult because, during the course of the experiment, not only the weight but also the number of animals varies, owing to the intervening deaths. Estimation of the intensity of pulmonary lesions would be the most direct means of evaluation. However, it has been used until now only as a qualitative complement of the other, more objective, methods.

The T_{50} determination is considered by many authors as a completely satisfactory and adequate instrument (6). In effect, very good results have been obtained by this method. It may be observed, however, that it is based on evaluation of percentages and not of individual quantitative data; moreover, it may be biased by the toxicity of the drug itself. The last objection is also valid but to a higher degree, in so far as the weight curve is concerned, because it is the first to be affected by toxic factors.

The most specific means of evaluation is undoubtedly the intensity of the pulmonary lesions because it is relatively less dependent on factors not correlated with the infection or with the action of drugs on the infection itself. The pure subjective character of this method has always prevented its extensive use. The purpose of the present report is to propose a method for the quantitative evaluation of pulmonary lesions, thus allowing potency comparisons between different antituberculous drugs.

During the course of experimental tuberculosis in mice, an enlargement and increase in weight of lungs were observed (1). The weight of the spleen also shows important variations, but these are very irregular. Furthermore, it may be noted that lungs are selectively affected in experimental mouse tuberculosis.

[1] From the Laboratorio di Microbiologia, Istituto "Carlo Erba" per Ricerche Terapeutiche, Milan, Italy.

During a series of experiments for testing antituberculous activity *in vivo* of some isoniazid derivatives (7, 8), the enlargement of lungs seemed to be correlated directly with the intensity of lesions and, inversely, with the drug dosage. Therefore, comparison was first made between the dry weight of healthy lungs and of lungs of infected and untreated animals. The intensity of lesions, subjectively evaluated by a different number of pluses (from 0 to 5 plus) was then checked by the dry weight of the same organs. As the agreement between subjective estimation and objective evaluation was good, experiments were made in order to test whether the weight differences in lungs of animals treated with different amounts of active drugs could be used for a quantitative determination of their potency.

EXPERIMENTAL

Albino mice which weighed 17 plus or minus 1.5 gm. were used. Lots of 20 animals were prepared, and care was taken to have a corresponding distribution of weights in the different groups. Ten males and 10 females were present in each group. The animals were distributed in numbers of 10 for each cage and kept in a room at a constant temperature (24°C.). All of the animals were given a diet with the following composition: corn meal, 52 per cent; maize meal, 17 per cent; casein, 15 per cent; corn bran, 5 per cent; dry yeast, 5 per cent; salt mixture of Osborne and Mendel, 4 per cent; cod-liver oil, 2 per cent. To every 100 gm. of diet, 2 gm. of wheat-germ oil were added.

The infection was produced by intravenous injection of 0.2 mg. (wet weight) of *M. tuberculosis* H37Rv, taken from a fifteen-day-old culture in Youmans' modification of Proskauer and Beck's medium (5), suspended in 0.2 ml. of sterile saline. The suspension density was always determined and adjusted turbidimetrically on a Coleman spectrophotometer at 650 mμ.

As soon as possible after death, the thorax and abdomen of the animals were opened wide and the carcasses were then kept in 10 per cent formol. When all of the control animals had died, usually thirty to thirty-four days after infection, all of the surviving treated mice were killed by ether; their abdomens and chests were opened and were also immersed in formol for eight days. Following this, they were thoroughly washed under running water, the lungs were carefully isolated from heart and vessels, dried by squeezing between two sheets of filter paper, and placed in a desiccator over calcium chloride until reaching constant weight. Final weights were then recorded and used for calculations.

RESULTS

Comparison between healthy and infected animals: Two groups of 20 animals were infected as described above, and a corresponding number of mice were used as controls. At the end of the experiment, 37 animals for each group could be used for calculation. Results and calculation of significance are summarized in table 1.

As may be seen from the table, the difference between the weights of lungs of normal and infected animals is highly significant.

Experiments with treated animals: The drugs were administered to the treated animals uniformly dispersed in the diet. In view of the fact that previous experiments showed the diet intake of mice in twenty-four hours to be equivalent to approximately one-tenth of body weight, the amount of drug per 100 gm. of diet was considered as the amount administered per kg.

Three drugs were studied, namely, isoniazid; isoniazid methanesulfonate, calcium salt; and isoniazid parabenzaldehyde. The amounts of the different drugs added to 100 gm. of diet, calculated from their isoniazid content, were as follows:

Isoniazid: 1.25 mg.–2.5 mg.–5.0 mg.
Isoniazid methanesulfonate: 0.75 mg.–1.5 mg.–3.0 mg.
Isoniazid parabenzaldehyde: 2.5 mg.–5.0 mg.

The action of isoniazid was taken as a standard and the effect of the other drugs compared with it. The results obtained and statistical treatment of data are summarized in tables 2, 3, 4, and 5.

TABLE 1

COMPARISON BETWEEN THE LUNG DRY WEIGHTS OF NORMAL AND INFECTED MICE AND CALCULATION OF SIGNIFICANCE OF THE DIFFERENCE

TREATMENT	NUMBER OF MICE	D.f.	MEAN LUNG WEIGHTS IN MG.	SUM OF SQUARES
Normal	37	36	41.5	1,184.25
Infected	37	36	171.5	75,405.25
		Sum = 72	Difference = 130	Sum = 76,589.5

$t = 17.6 \qquad P < 0.001$

TABLE 2

COMPARISON OF THE EFFECT OF DIFFERENT DOSAGES OF ISONIAZID AND ISONIAZID METHANESULFONATE ON THE WEIGHT OF LUNGS OF MICE INFECTED WITH M. TUBERCULOSIS H37Rv

DRUGS	ISONIAZID			ISONIAZID METHANESULFONATE		
Dosage mg. per 100 gm. of diet	1.25	2.5	5.0	0.75	1.5	3.0
Number of mice	19	19	20	19	20	20
Mean lung weight (mg.)	183.1	99.8	51.2	158.5	97.85	45.25

As will be seen in tables 3 and 5, the differences relating to "dosage" are significant, whereas those of "parallelism," "combined curvature," and "opposite curvature" are not. Calculation of the relative potency of two drugs is therefore possible, provided a suitable dosage is used.

If too small or large doses are administered, the effects obtained are not proportional to the amount of the drug and the potency evaluation is no longer valid.

When the dosage conditions which allow a linear regression are satisfied, calculation of the relative potencies of two drugs may be made on the basis of the usual formula:

$$R = I\frac{D}{B} \qquad M = \text{antilog } R$$

Where I is the logarithm of the ratio between the dosage for adjacent groups of either preparation, D is the difference between the total response (weights) of all the test groups and the total response (weights) of all the standard groups,

TABLE 3

STATISTICAL TREATMENT OF DATA REPORTED ON TABLE 2

SOURCES OF VARIATIONS	D.f.	SUM OF SQUARES	MEAN SQUARE	F	P
Substances	1	4,118.4	4,118.4	2.105	$0.2 > P > 0.1$
Dosage	1	294,031.2	294,031	150.291	$P < 0.001$
Parallelism	1	2,268.5	2,268.5	1.159	Not significant
Combined curvature	1	2,680.0	2,680.0	1.369	Not significant
Opposite curvature	1	1,430.8	1,430.8	0.731	Not significant
Error	111	217,165.1	1,956.4		
Total	116	521,694.0			

TABLE 4

COMPARISON OF THE EFFECT OF DIFFERENT DOSAGES OF ISONIAZID AND ISONIAZID PARABENZALDEHYDE ON THE WEIGHT OF LUNGS OF MICE INFECTED WITH M. TUBERCULOSIS H37Rv

DRUGS	ISONIAZID		ISONIAZID PARABENZALDEHYDE	
Dosage mg. per 100 gm. of diet	1.25	2.5	2.5	5.0
Number of mice	19	19	19	20
Mean lung weight (mg.)	183.1	99.8	170.25	64.8

TABLE 5

STATISTICAL TREATMENT OF DATA REPORTED IN TABLE 4

SOURCES OF VARIATIONS	D.f.	SUM OF SQUARES	MEAN SQUARE	F	P
Substances	1	11,448.0	11,448.0	5.295	$0.05 > P > 0.01$
Dosage	1	178,132.0	178,132.0	82.392	$P < 0.001$
Parallelism	1	2,453.0	2,453.0	1.134	Not significant
Error	73	157,829.0	2,162.0		
Total	76	349,862.0			

and B is the difference between the total response (weights) of the groups with the highest dosage (test and standard) and of the groups with the lowest dosage (test and standard).

For the comparison between isoniazid and isoniazid methanesulfonate, where isoniazid is taken as a standard:

$$R = 0.04361$$
$$\text{antilog } R = M = 1.1056$$

M indicates the potency ratio for the dosage actually used in the experiment. In order to calculate the relative potency of the two drugs, this must be multiplied by the ratio of the dosage for the two drugs. In the present case, since the ratio isoniazid/isoniazid-methanesulfonate is 5:3, the potency of isoniazid methanesulfonate in comparison to isoniazid is:

$$P = 1.1056 \cdot 5:3 = 1.84$$

thus, in the experiment under consideration, isoniazid methanesulfonate appears to be 1.84 times as potent as isoniazid. Considering now the relationship between isoniazid and isoniazid parabenzaldehyde, the following result is obtained:

$$R = 0.07631$$
$$\text{antilog } R = M = 1.192 \qquad \text{isoniazid/isoniazid parabenzaldehyde} = 1:2$$
$$P = 1.192 \cdot 1:2 = 0.596$$

Therefore, isoniazid parabenzaldehyde is 0.596 times as potent as isoniazid.

COMMENT

There is a very great difference between the weights of lungs of healthy mice and mice of the same age infected intravenously by virulent *M. tuberculosis*. The lungs of the latter are very much enlarged and increased in weight. When infected animals are given antituberculous drugs, a decrease in lung weight parallel to a decrease in the number of lesions, subjectively estimated and proportional to the dosage administered, may be observed and evaluated quantitatively. The relationship between dosage and lung-weight decrease is linear within the range of effectiveness of the drug under examination; that is, over a maximum given dosage, no additional effects may be obtained; and, under a minimum given dosage, none can be detected. A quantitative evaluation of the relative potencies of different drugs may be made within this range. In order to obtain constant results, the experimental conditions must be very carefully controlled.

Some isoniazid derivatives were compared in these experiments, and isoniazid methanesulfonate showed a higher activity than isoniazid itself. In order to learn the reason for this very interesting phenomenon, a detailed study was made on the metabolism of both compounds (8). The interest aroused by the high *in vivo* activity of isoniazid methanesulfonate has been increased by its low toxicity (7).

As mentioned before, the method for evaluating antituberculous activity shown here seems to offer some advantages in comparison with the determination of T_{50} because of its more pronounced specificity and because it does not utilize percentages but individual numerical data. Like T_{50}, it is completely objective

and permits quantitative evaluation of a phenomenon which has been appraised only subjectively until now.

SUMMARY

A sharp increase in lung-weight is observed during experimental tuberculosis in mice infected intravenously. This phenomenon is counteracted by the administration of antituberculous drugs; within certain limits, the action of these is directly proportional to the dosage used.

A method for the quantitative evaluation of antituberculous activity has been described and statistically elaborated on this basis.

Isoniazid and two of its derivatives were submitted to this test and showed significant differences in activity as compared with the parent substance; in fact, isoniazid methanesulfonate is more active, and isoniazid parabenzaldehyde less active, than isoniazid.

SUMARIO

De la Justipreciación Cuantitativa de la Actividad de las Drogas Antituberculosas en la Tuberculosis Murina Experimental

Durante la infección tuberculosa experimental por vía intravenosa en los ratones obsérvase un aumento decidido del peso del pulmón. Ese fenómeno es contrarrestado por la administración de medicamentos antituberculosos, cuya acción, dentro de ciertos límites, se halla en proporción directa a la dosis usada.

Partiendo de esa base, se describe y elabora estadísticamente un método para la justipreciación cuantitativa de la actividad antituberculosa.

La isoniacida y dos de sus derivados fueron sometidos a esa prueba, revelando los últimos diferencias importantes en su actividad, comparada con la de la substancia matriz; en efecto, el metansulfonato de la hidracida del ácido isonicotínico es más, y el parabenzaldehido de la hidracida del ácido isonicotínico menos, activo que la isoniacida.

RESUME

De l'évaluation quantitative de l'activité des préparations antituberculeuses sur la tuberculose expérimentale de la souris

Un net accroissement du poids du poumon est observé au cours de l'infection tuberculeuse intraveineuse expérimentale de la souris. Ce phénomène est combattu par l'administration de produits antituberculeux; l'action de ces préparations est, dans certaines limites, directement proportionnelle aux doses utilisées.

L'auteur décrit une méthode permettant l'évaluation quantitative de l'activité antituberculeuse et une statistique fondée sur cette base est présentée.

L'isoniazide et deux de ses dérivés ont été soumis à ce test qui a permis d'observer des différences d'activité appréciables du point de vue statistique, par comparaison avec la substance originale. En fait, l'hydrazide métansulfonate de l'acide nicotinique est plus active et l'hydrazide parabenzaldéhyde de l'acide isonicotinique moins active que l'isoniazide.

Acknowledgment

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Case Reports

PULMONARY CAVITATION DUE TO HISTOPLASMA CAPSULATUM[1, 2]

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INTRODUCTION

In making a definitive diagnosis of tuberculosis, it is necessary to find the tubercle bacillus in the sputum or to isolate the organism from body fluids by culture or animal inoculation. Likewise, the diagnosis of histoplasmosis can be established only by demonstrating the fungus in a smear, section, or in isolation by culture. In only a relatively small percentage of suspected pulmonary cases is it possible to demonstrate the organism before death. Charr reports that the longest survival after a diagnosis of clinical histoplasmosis has been made is approximately two years (1) but, according to Hodgson, Weed, and Clagett, one patient survived more than five years and two others were apparently cured after four years (2).

In the case herein reported the patient is still alive almost three years following the recovery of *Histoplasma capsulatum* in culture from the sputum and four years after the onset of symptoms.

CASE REPORT

J. A. McK., a 52-year-old white male, was first seen in the tuberculosis clinic on October 11, 1949, when he came for a chest roentgenogram because of pain in his chest. He was born in Meriwether County, Georgia, lived in Texas for three years during childhood, and had lived in Columbus, Georgia, for five years immediately preceding his present illness. He gave no history of tuberculous contact, and his family and past history were noncontributory. He worked as a laborer on a pipe line in Macon, Georgia, for two years before coming to Columbus and had been a barroom attendant in Phenix City, Alabama, a bordering town, prior to admission to the clinic.

His initial chest film was read as far advanced pulmonary tuberculosis with bilateral cavitation. He was recalled on October 21, 1949, for an interview. His chief complaint at this time was pain of one month's duration in the upper chest region, hoarseness for two weeks, and production of blood-streaked sputum. Sputum was negative on direct examination and culture for tubercle bacilli on October 24 and 25, 1949. Sputum cultures for fungi were negative on November 5, 1949, and January 5, 1950. Skin tests with purified protein derivative (PPD) were negative in first strength and weakly positive in second strength. Histoplasmin, 1 to 1,000 dilution, was weakly positive, while blastomycin and coccidioidin reactions were negative.

Roentgenograms of the chest on November 9 and December 30, 1949, showed no change in the size of the cavities although there was some increased peribronchial infiltration in the upper halves of both lung fields.

The patient was sent to Emory University Hospital, Atlanta, Georgia, for bronchoscopy on January 23, 1950, which revealed a diffuse tracheobronchial infection and scarring of

[1] From the Muscogee County Department of Public Health, Columbus, Georgia.

[2] Presented, in part, before the Third District Medical Society of Georgia, November 1950, and the Laboratory Section of the Georgia Public Health Association, May, 1951.

the vocal cords. Laryngeal biopsy was said to show tuberculosis. All sputum specimens and bronchial washings were, however, repeatedly negative for tubercle bacilli on direct examination and culture. The tuberculin reaction (PPD, first strength) was read as positive. Application was made to Battey State Tuberculosis Hospital. Roentgenograms made on March 11, 1950, showed no change in the chest condition.

The patient was admitted to Battey State Hospital in Rome, Georgia, on March 28, 1950. His chief complaints were hoarseness and progressive loss of voice for the preceding six months, pain in the chest anteriorly, and cough with scanty, mucoid, blood-streaked sputum. He had lost 17 pounds since his first clinic visit. Physical examination revealed a 108-pound white male who had dyspnea, laryngeal wheeze, and inability to speak above a hoarse whisper. Moderate congestion of the tonsillar and posterior pharyngeal regions, redness of the laryngeal structures, and ulceration of the epiglottis were noted. The trachea was deviated to the right, movement was impaired over the upper right chest anteriorly and posteriorly, and resonance was slightly impaired over the upper portions of the chest.

FIG. 1. Roentgenogram of the chest. Note massive cavities in both upper lung fields, with considerable peribronchial infiltration. Film taken on December 30, 1949.

Kronig's isthmus was narrowed on the right. The heart was normal and blood pressure was 100 systolic, 70 diastolic. The pulse was 90 per minute. There was moderate clubbing of the fingers and toes. Posterior cervical and axillary lymph nodes were palpable.

Laboratory data included a negative serologic test for syphilis (Kahn), hemogram, urinalysis, and stool examination for blood. The sedimentation rate was 20 mm. per hour. The sputum was repeatedly negative for tubercle bacilli on direct examination, culture, and guinea pig inoculation.

Direct laryngoscopy showed edema of the arytenoids and false vocal cords. The vocal cords were not visualized, due to extensive edema. Fluoroscopy and roentgenograms showed no change from the condition previously seen.

The patient received 0.5 gm. of streptomycin intramuscularly daily from March 30 to May 16, 1950, when he left the hospital against advice. At this time his diagnosis was pulmonary tuberculosis, far advanced, and tuberculous laryngitis. He was considered to be unimproved.

He was seen again in the clinic at Columbus on August 17, 1950. Chest films on this date and on October 10, 1950, showed no remarkable changes.

Sputum which was inoculated onto beef infusion blood agar on August 22, 1950, grew a small cerebriform brick-red colony. This was transferred to Sabouraud's medium and incubated at room temperature. Typical white cottony colonies developed, from which were

FIG. 2. Roentgenogram of chest taken March 3, 1953. There is little change in the appearance of the lung fields over a 38-month period.

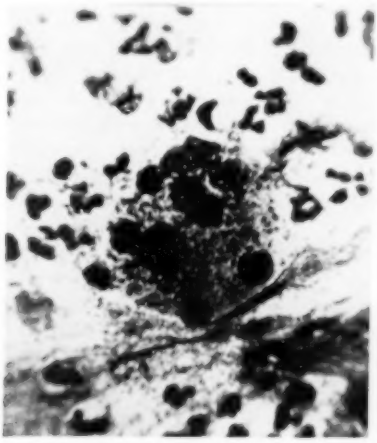

FIG. 3. Photomicrograph of parasitized mononuclear cell from sputum on direct smear, characteristic of *Histoplasma capsulatum*. Wright's stain.

demonstrated the diagnostic large tuberculate chlamydospores of *Histoplasma capsulatum*. Other cultures on September 20 and 22, 1950, were positive for histoplasma. Subsequently, after diligent search, parasitized mononuclear cells were seen on sputum smears stained with Wright's stain.

The patient was still quite hoarse and went to Atlanta, Georgia, to a private clinic on October 2, 1950, where a tracheotomy was performed and a tracheotomy tube left in the opening. He had considerable relief after the operation. His laryngeal symptoms had disappeared when he was seen in December, 1950, and he had gained 11 pounds. At this time a complement fixation for histoplasma was positive in dilution 1:32. Bone marrow biopsy from the crest of the ilium taken on December 11, 1950, was negative for histoplasma.

He returned to Atlanta in July, 1951, and the tracheotomy tube was removed. Roentgenograms were taken at intervals until March 4, 1953. Examination at this time showed a small sinus tract in the tracheotomy wound, but the patient had no difficulty in speaking. His roentgenograms since July, 1951, have remained essentially unchanged, although slight decrease in the size of the cavities was thought to have occurred. Sputum on March 4, 1953, was still positive for *Histoplasma capsulatum* on culture and direct smear. Culture for tubercle bacilli was negative. His weight has remained between 111 and 119 pounds.

The patient received no definitive treatment for his condition other than tracheotomy and a course of streptomycin while at Battey Hospital, following which he showed no improvement. He is still living and is ambulatory. He is unemployed at present.

COMMENT

There is no characteristic roentgenographic appearance of the lesions of pulmonary histoplasmosis. Heretofore only four cases have been reported with pulmonary cavitation (1, 2), and the cavitation may not have been due solely to histoplasmosis in at least two of the four cases. Thus pulmonary cavitation is a rare phenomenon in this disease. A negative histoplasmin skin test does not preclude the presence of histoplasmosis.

As evidence against this patient's having concurrent tuberculosis there were at least six smears and cultures which were negative for tubercle bacilli, no improvement with streptomycin therapy, and the fact that the pathologic appearance of the various granulomata are quite similar to that of histoplasmosis (3).

Until the present, no proved case of histoplasmosis has been reported from Georgia, although 139 cases were reported by Hodgson, Weed and Clagett in 1950 (4), and approximately 42 cases were reported since from twenty-four states, the District of Columbia, and eighteen foreign countries. Long and Stearns have described an area of the United States in which pulmonary calcifications occurred most frequently (5). This area included the northwest corner of Georgia. Palmer, in his classic paper, demonstrated that in those states in which the rate of pulmonary calcification is high the reactions to histoplasmin are also high, histoplasmosis probably being the underlying cause of a considerable portion of the calcifications noted (6).

The epidemiology of histoplasmosis is still unknown for the most part although animals have long been known to be infected, and Emmons has isolated the fungus from the soil near the entrance to burrows of infected rats (7). A variety of animals have been found to be infected with *Histoplasma capsulatum* (8). It is quite possible that animal-to-man infection with histoplasma may occur, as it does in Q fever and brucellosis, or it may be spread, as in coccidioidomycosis, as an animal-to-soil-to-man infection.

In support of the last-named hypothesis, Grayston and Furcolow have reported a series of epidemics of histoplasmosis in which the infections occurred through the inhalation of air-borne organisms, *Histoplasma capsulatum* being present in the soil at the point source of most of the epidemics (9).

It is important to note that, when lesions of the chest are found resembling tuberculosis and when repeated search for tubercle bacilli is fruitless, examination for fungi may be rewarding. Such examinations should be attempted only on fresh specimens of sputum, gastric contents, and bronchial washings, and should consist of a thorough search of stained

preparations as well as culture for the intracellular parasite, giving ample time for the fungus to grow (10).

Skin reactions may be helpful but, as in the case of the tuberculin test, a positive or negative reaction does not furnish conclusive proof of the presence or absence of the disease. As yet no drugs have proved effective in combating histoplasmosis.

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PULMONARY CRYPTOCOCCOSIS[1]

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INTRODUCTION AND REVIEW OF THE LITERATURE

The relatively high incidence of pulmonary cryptococcosis or the history of previous pulmonary disease associated with central nervous system cryptococcus infections is now well recognized and has led the majority of writers to believe that the respiratory tract is the portal of entry (1, 2). Pneumonitis due to *Cryptococcus neoformans* without associated central nervous system involvement, however, has been rarely diagnosed. Berk and Gerstl (3) in 1952 reviewed the literature on this subject and collected only five previous cases and reported a sixth. Three other cases of cryptococcosis, limited to the lungs, have been found in the literature available to us (4, 5).

Cox and Tolhurst (2) have suggested that cryptococcosis limited to the lungs is probably more common than the number of reported cases would indicate. They believe that many such infections are relatively mild in nature and heal spontaneously without metastasizing to the central nervous system. The actual incidence of extra-central nervous system infections continues to remain unknown because of the lack of readily performed and accurate diagnostic tests for cryptococcosis.

The signs and symptoms of cryptococcosis depend upon the nature of the disease of the lung. The patients who had tumor-like lesions were asymptomatic, and the disease was discovered on routine roentgenographic examination. Symptoms were always present in the pneumonic forms of the disease, but were nonspecific and generally mild. The most common was a dry nonproductive cough. Sputum, if present, was generally mucoid, and in two cases was blood tinged. Chest pain was noted in two of the nine cases. There was usually a low-grade fever varying between 99.0° and 101.0°F., accompanied by some degree of malaise. The patients appeared well on physical examination. The signs of pulmonary pathology were usually those suggestive of consolidation of the affected side, but in several cases were completely absent.

Routine laboratory studies were noncontributory. There was a leukocytosis in three of the four cases in which leukocyte counts were reported. The differential count was either normal or showed a predominance of polymorphonuclear leukocytes. The pulmonary roentgenographic findings varied and were not diagnostic. Several types of lesions have been reported. These included a fairly dense and massive shadow resembling a tumor (toruloma), small disseminated nodular shadows resembling tuberculosis, and a patchy pneumonitis with a predilection for the lung bases. Of the nine cases reported, four had a toruloma, three had a pneumonitis, and two had small nodular lesions. These pulmonary findings correspond closely to those described as occurring concomitantly with central nervous system cryptococcosis.

The prognosis varied, depending upon the type of lesion. All of the patients with torulomas underwent a lobectomy or pneumonectomy of the involved lung and were alive at the time the cases were reported. Two of the five patients with the more diffuse type of lung involvement died. One expired from asphyxiation due to exuberant granula-

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tion tissue which occluded the lumen of the major bronchi (6), and the other succumbed to a severe cryptococcus pneumonia (7). Of the three remaining patients, one had regression of the disease and was reported to be in good health one year later (8). One patient continued to have signs, symptoms, and roentgenographic abnormalties fifteen months after the diagnosis was made (9). There was no reported follow-up on the third patient (4).

No chemotherapeutic measures which have been used to date have been effective against cryptococcosis. Surgical extirpation of the involved lobe has been successful in the toruloma variety of the infection (3).

The purpose of the present report is to present in greater detail a case of pulmonary cryptococcosis which was briefly cited in a survey study previously published (10).

CASE REPORT

H. S., a 47-year-old male of Mexican extraction, entered the hospital on June 12, 1951.

History: Six months prior to admission the patient noticed a small erythematous, crusted papule below the right eye. This slowly enlarged until the major portion of the right cheek and lower eyelid was involved. Three months prior to admission similar lesions appeared on the back, anterior chest, and behind the ear. There was no pruritis but the lesions were painful at night.

Physical examination: The patient was found to be well developed and well nourished, with the abnormal findings limited to the skin. A scaling, crusted, moist, erythematous plaque, 3 cm. in diameter, with an irregular, sharply demarcated border was present on the lower right eyelid and adjacent malar eminence. There were five similar lesions, varying from 0.5 to 1.5 cm. in diameter, over the trunk and the scalp. A tentative diagnosis of pemphigus vulgaris was made.

Admission laboratory studies: Urinalysis was normal. The leukocyte count was 3,350 per cu. mm. with a differential of 55 per cent neutrophils, 36 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils. The erythrocyte count was 5.4 million per cu. mm., and the erythrocyte sedimentation rate was 2 mm. per hour. Serologic tests for syphilis were negative. A chest roentgenogram was normal. Biopsy of the lesion below the right eye was interpreted as being compatible with pemphigus vulgaris, as were subsequent biopsies of other sites.

Course in the hospital: Shortly after the patient was admitted to the hospital, numerous bullous lesions appeared over the entire torso. They were most prominent on the face, neck, and upper chest. Corticotropin therapy was initiated on July 26, 1951, because of the continued appearance of new bullae. The corticotropin was administered intramuscularly, 80 mg. daily in divided doses. There was no improvement after two weeks and the drug was discontinued. Cortisone therapy was then initiated on August 7, 1951. The dose was 200 mg. intramuscularly daily. There was no significant improvement during the next two months. The dose of cortisone was gradually reduced and the drug was discontinued entirely on October 10, 1951.

A definite exacerbation of the pemphigus occurred within the two weeks following the cessation of the cortisone. On October 23, 1951, the patient developed a fever of 101°F. and a mild nonproductive cough. A roentgenogram of the chest at this time revealed diffuse, soft infiltrates in the right lung field in the region of the first intercostal space anteriorly and along the cardiophrenic angle (figure 1). Alpha- and beta-hemolytic streptococci were cultured from the sputum during the last week of October. Attempts to detect the presence of tubercle bacilli on numerous occasions by smears and cultures were unsuccessful. The leukocyte count was 8,200 per cu. mm. with 90 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes, and 4 per cent monocytes.

During this period the patient felt reasonably well, but his temperature rose to 102°F. daily. The cough continued to be nonproductive. Another roentgenogram of the chest on October 28, 1951, revealed an increase in the density of the pneumonic process at the cardiophrenic angle on the right. A new area of infiltration was seen to overlie the anterior edge

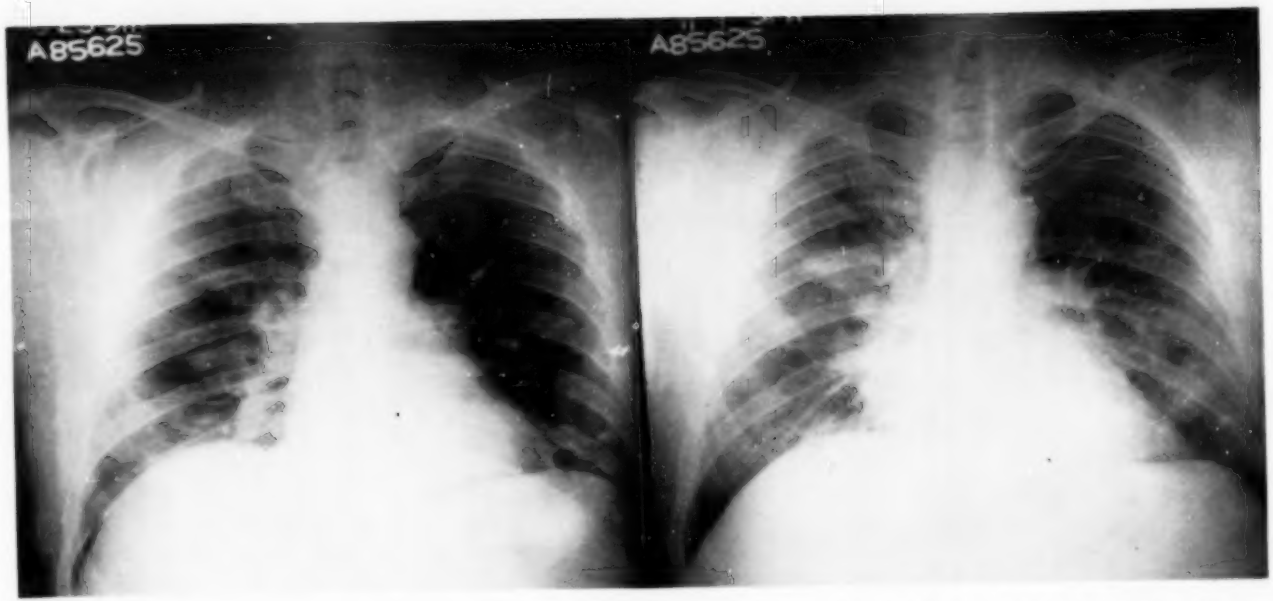

FIG. 1. (Left) Chest roentgenogram of October 23, 1951, showing diffuse soft infiltrate in the right lung field in the region of the first intercostal space anteriorly, and also along the cardiophrenic angle beneath the hilum.

FIG. 2. (Right) Chest roentgenogram of November 1, 1951, showing increase in the pneumonic infiltrate in the right lung field and several areas of hazy increased density in the left lung field.

of the third rib. The left lung field remained clear. The clinical picture and roentgenographic findings were compatible with primary atypical pneumonia, and the patient was given 2 gm. of chlortetracycline (Aureomycin) daily from October 28, 1951, to November 12, 1951. His temperature rose to 103.8°F. on October 30, 1951, but then decreased and returned to normal on November 3, 1951. Roentgenographic examination of the chest during this time showed an increase in the pneumonic infiltrates in the right lung field, and, in addition, there were several hazy areas of increased density in the left lung field (figure 2).

India ink preparations of the sputum on November 12, 1951, revealed encapsulated organisms morphologically identical with *Cryptococcus neoformans*. This organism was isolated from the sputum which was inoculated on Sabouraud's dextrose agar incubated at 37°C. Saline suspensions of these cultured organisms were injected intraperitoneally into 3 mice. All died within two weeks, and the organism was recovered from the central nervous system by smear and culture. Chlortetracycline therapy was discontinued on November 12, 1951, when the etiology of the pneumonitis was recognized and no therapy was administered thereafter except bed rest.

Cerebrospinal fluid examinations were performed on November 19, 1951, and December 3, 1951. The pressure of the fluid was normal on both occasions and there was no increase in the cells or protein. The chloride and sugar concentrations were normal. No organisms were found in the cerebrospinal fluid by smear, culture, animal inoculation, or india ink mounts.

There was definite roentgenographic evidence of resolution of the pneumonitis on November 27, 1951. Improvement continued until January 2, 1951, when complete resolution had occurred and the chest roentgenogram was normal. *Cryptococcus neoformans* was repeatedly isolated from the sputum during this period but, on January 9, 1952, it could no longer be demonstrated. Frequent sputum examinations for this organism during the past year have been negative.

COMMENT

This case of pulmonary cryptococcosis is of particular interest because the disease developed while the patient was under medical surveillance. The disease appeared to progress for one month, after which it underwent slow resolution during the succeeding six weeks. The signs and symptoms were minimal, and at no time did the patient appear acutely ill. The symptoms corresponded with those recorded for similar cases.

All the criteria for establishing the diagnosis of pulmonary cryptococcosis were fulfilled in this case. They were: demonstration of the organism in the sputum on numerous occasions during the period of active disease; proof that the organism was pathogenic; disappearance of the organism concurrent with resolution of the pneumonic process; and failure to recover other known pathogenic bacteria or fungi.

Cryptococcosis is considered to be of endogenous origin, and poorly understood predisposing factors apparently play an important part in the development of the disease. The presence of a lymphoblastoma, particularly Hodgkin's disease, has frequently been observed. Cryptococcosis has also been associated with other debilitating diseases such as tuberculosis, moniliasis, and histoplasmosis (11). Its development in a patient with pemphigus has not been reported. It is difficult to evaluate the significance of pemphigus as a predisposing factor, and this is particularly true since the infection spontaneously resolved in spite of the progression of the dermatosis. It is believed that the cortisone was a more important predisposing factor in the development of cryptococcosis in the present case. This opinion is based on the fact that the signs and symptoms of the pneumonitis developed during the period of endocrine imbalance immediately following a long course of cortisone therapy. It is now a well-recognized fact that endogenous infections develop during cortisone therapy. Tuberculosis has been the most common and serious of these. Fulminating systemic mycotic infections have also been reported.

Again it must be emphasized that the symptoms of pulmonary cryptococcosis are not characteristic nor are the roentgenographic findings diagnostic. In view of the lack of readily available diagnostic procedures, it is important that the clinician consider cryptococcosis in all undiagnosed protracted pneumonias.

SUMMARY

A case of cryptococcosis localized to the lung, which developed in a patient shortly after discontinuation of long-term therapy for pemphigus vulgaris, is reported. The disease extended over a ten-week period and resolved spontaneously. The role of cortisone in the development of the present case is discussed. Nine previously reported cases of localized pulmonary cryptococcosis are reviewed.

SUMARIO

Criptococcosis Pulmonar: Presentación de un Caso

El caso comunicado de criptococcosis localizada en el pulmón apareció en un enfermo poco después de discontinuar una terapéutica a largo plazo por pénfigo vulgar. La dolencia abarcó un período de diez semanas y se resolvió espontáneamente. Discútese el papel de la cortisona en la producción del caso. Repásan 9 casos descritos anteriormente de criptococcosis pulmonar localizada.

RESUME

Mycose du poumon (Cryptococcus histoliticus): Observation d'un cas

Communication sur une mycose pulmonaire due au *Cryptococcus histoliticus* qui s'est manifestée chez un patient, peu de temps après l'interruption d'un therapie prolongée par le steroide dans un cas de pemphigus commun. L'affection s'est prolongée pendant dix semaines et a disparu spontanément. Le rôle de la cortisone dans le développement de ce cas est commenté. Neuf cas de cryptococcose pulmonaire localisée sont analysés.

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Editorial

Pneumothorax Induction by Lung Puncture or "Orthodox" Technique?

In 1936, Tchertkoff (Quart. Bull. Sea View Hosp., 1936, *1*, 398) revived the old statement by Morgan that the first intrapleural manometric readings in an artificial pneumothorax are those obtained by injuring the lung. Tchertkoff advocated that every initial pneumothorax is first a traumatic one. In 1948, with Selikoff and Robitzek (Dis. of Chest, 1948, *14*, 475), he developed a new method for the induction of artificial pneumothorax which consists in a deliberate puncturing of the lung with the needle attached to the syringe with the anesthetic solution or saline. Although the use of this technique has not become widespread, some investigators recommend it as "a simple, safe and reliable procedure" (Moyes, E. N., and Scott, J. K.: Lancet, 1952, *1*, 1278).

The fact is well known that the induction of pneumothorax in a certain percentage of cases is followed by the development of so-called spontaneous or, more precisely, an accidental pneumothorax, which manifests itself in an excessive accumulation of air in the pleural cavity. The majority of writers consider the accidental pneumothorax with its possible untoward effects as a complication which should be avoided as far as possible. Many different factors were made responsible for the development of accidental pneumothorax as, for instance, weak spots in the visceral pleura, tearing of adhesions, presence of subpleural caseous foci, or rupture of emphysematous blebs. However, according to the majority of authors, the most important factor responsible for this complication is the direct trauma to the lung tissue during the induction of pneumothorax. The percentage of accidental pneumothoraces during the induction ranges in wide limits, from 0 to 21 per cent, according to various writers.

The majority of writers consider an accidental pneumothorax preventable by using a careful technique. Hartmann (Tuberkulosearzt, 1949, H4, 217) and Markgraf (Tuberkulosearzt, 1948, H11, 743) introduced a special type of blunt needle with the orifice on the side going to the tip of the needle. Markgraf elaborated a special technique by which he inserts the needle perpendicularly and, after reaching the pleura, turns it to oblique position. The blunt tip of the needle pushes the lung, simultaneously permitting the aspiration of several milliliters of air from the tube into the potential pleural space through the orifice on the side of the needle, thus giving the first pleural readings. He claims that with this technique he has not seen a single case of accidental pneumothorax in a very large number of initial pneumothoraces.

In contrast with the foregoing data are those of Tchertkoff and his associates, who conducted a study of their own. They claimed that, in each of the cases in which pleural readings were obtained by inserting the needle into pleural space without giving any air or after giving small amounts (approximately 100 ml.), a progressively increasing pneumothorax space was demonstrated by fluoroscopy

and roentgenography. Tchertkoff and his associates concluded that every initial pneumothorax is first a traumatic one and that, when air is given, the collapse is always greater than might be expected from the amount of air introduced. On the basis of their experiments, Tchertkoff and associates introduced the so-called traumatic induction of artificial pneumothorax by a deliberate puncturing of the lung and claimed that this technique of pneumothorax induction is a safer and more reliable procedure than the conventional technique.

The experiment of Tchertkoff and co-workers was repeated by Dooneief and Piccagli (Am. Rev. Tuberc., 1949, *60*, 557), who obtained different results. They concluded that "... the conventional method of pneumothorax induction with a blunt needle does not cause trauma to the lung of sufficient degree to permit escape of air demonstrable by available roentgenographic methods."

It may be seen that the majority of investigators consider the accidental pneumothorax as a preventable complication, not as a rule. Entertaining such a view, the present writer believes that the creation of pneumothorax can be satisfactorily explained by mechanisms other than trauma to the lung. At the very moment when the tip of the needle (or the part of the needle indicated in Markgraf's technique), after piercing the parietal pleura, comes into contact with the potential pleural space, aspiration of several milliliters of air from the tube occurs, which manifests itself in the simultaneous drop of manometric pressure. "A little pulling back of the needle, or a gentle pushing forward" in order to obtain the space are not necessary, the readings may be obtained immediately without any manipulations which would cause traumatization. Markgraf refers to the interesting statement by Reinhardt that touching of visceral pleura by the tip of the needle stimulates the active contraction of the underlying pulmonary tissue, which contributes to the aspiration of the air from the tube and prevents the injury to the lung.

The present writer believes that the pneumothorax induction which he uses may represent the evidence of the correctness of the view that the initial readings are those obtained by the aspiration of air from the tube, not by the injury to the lung. The valve with three openings is connected with a 2 cc. syringe (upper opening) filled with 1 to 2 cc. of anesthetic solution; the lower part, with a regular 18-gauge needle; the lateral, with the tube, which in its turn is connected with a pneumothorax machine. After the local anesthesia, the 18-gauge needle, which through the valve is in connection with the syringe, is being inserted in a routine way and gently pushed forward, millimeter after millimeter piercing the layers of the thoracic wall. The patient is instructed to breathe superficially (taking a deep breath is considered a poor procedure); no pulling back and forth with the needle is permitted. In the very moment when the tip of the needle reaches the potential space, the sudden aspiration of fluid and fall of the piston occurs and, if there is air above the fluid in the syringe, this air will be aspirated as well. In this moment the valve is being turned and connected with the manometer, which invariably shows a reading due to further aspiration of the air from the tube.

If the fall of fluid in the syringe does not occur it means that:

(*1*) The needle may be plugged. In order to prevent that after piercing of the skin, the needle is withdrawn, blown out, and reinserted in the same spot. (*2*) The needle has not reached the potential pleural space. (*3*) The pleura is adherent. (*4*) The tip of the needle is in the lung. In this case the fluid in the syringe does not fall at all, or may fall very slowly (never abruptly), but some air may be obtained in the syringe by pulling back the piston. When connected with the manometer, the "pulmonary readings" (minus 2, plus 2) may be obtained, as in one of the writer's cases.

In order to determine what percentage of initial pneumothoraces is followed by development of accidental (or traumatic) pneumothorax, the writer conducted a very careful study of 57 initial pneumothoraces, performed at Molly Stark Hospital between July 1, 1951, and December 31, 1952. The average amount of air given during the induction was approximately 300 ml.; on many occasions, less. A small, hardly visible space resulted (it is generally agreed that less than 150 ml. of air cannot be visualized by any roentgenographic technique), which occasionally could not be detected at all or only after examination in different projections. Any increase of the space over approximately 5 per cent after twenty-four hours was considered as evidence of an accidental pneumothorax. Accidental pneumothorax occurred in 5 instances (8.77 per cent) of initial pneumothoraces performed on 4 patients.

The results obtained confirm the writer's previous experience that with a careful technique for pneumothorax induction the increased accumulation of air in the pleural cavity, indicative of traumatic pneumothorax, is a relatively rare occurrence. As a rule, there is a direct relationship between the size of the space and the amount of air injected. It can be argued that a certain leakage of air into the pleural cavity cannot be excluded in cases where no traumatic pneumothorax could be diagnosed. Even if it were so, it should be negligible and not enough to increase the collapse significantly; and the role of the trauma, if any, in the creation of initial pneumothorax should be subordinate. According to the advocates of the traumatic theory of initial pneumothorax, in order to get readings, the needle should be pulled back after first being pushed in; otherwise, how can the initial reading be explained, the tip of the needle still being in the pulmonary tissue? Since with the technique of the present writer there is no pulling back, it is evident that mechanisms other than puncturing the lung are responsible for the initial manometric readings.

It is believed, therefore, that the creation of pneumothorax may be explained perfectly well without admitting the inevitable puncturing of the lung. The statement that every initial pneumothorax is first a traumatic one does not seem to be based on solid foundation and the technique of the deliberate puncturing of the lung in order to create a pneumothorax does not seem to be a sufficiently justified procedure. If in the course of pneumothorax induction the trauma occurs, it should be considered as a complication, not as a rule.

In contrast to the statement that a pneumothorax induction technique by lung puncture is a safe and reliable procedure, the present writer considers it to be potentially hazardous. For a certain time an opportunity was afforded to

the writer to observe and fluoroscope the cases of initial pneumothorax started by lung puncture and compare them with those started by him, using the needle with the hole on the side. The resulting impression was different from that which Tchertkoff and his associates have stated. Also one dramatic accident occurred within less than an hour after initial pneumothorax by lung puncture was started in a patient with a completely destroyed contralateral lung. As small as the needle for pneumothorax induction by lung puncture might be, if the trauma produced is sufficient to allow the air to escape into the pleural space, it will be large enough to let infection escape in the same space. The presence of peripheral cavitation, subpleural or peripheral foci, even not visualized on roentgenography, should always be kept in mind; the puncture of such foci may result in a contamination of pleural space. The amount of air entering through the hole in pulmonary tissue also cannot be controlled, and this may lead to a development of a tension pneumothorax which may endanger the patient's life in case of a destroyed or absent contralateral lung.

The present writer believes, therefore, that the pneumothorax induction technique by lung puncture is not sufficiently justified and hardly represents a safe and reliable procedure which could be recommended for routine use.

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Notes

THE EFFECT OF ISONIAZID ON GROWING AND RESTING TUBERCLE BACILLI

For an understanding of the antibacterial effect of isoniazid on tubercle bacilli, it is important to know whether this drug acts only on growing or also on resting bacteria. Clinical observations and laboratory findings reported by Mackaness and Smith[1] suggested that only growing bacteria are affected by the drug. The same conclusion is reached in the more direct experiments reported here, in which it is shown that isoniazid is bactericidal for tubercle bacilli when it is added to a culture medium which is adequate for their growth (in the absence of the drug) but is without effect on their viability when it is present in a medium which does not support growth.

The effect of isoniazid on growing and resting tubercle bacilli was studied in the following experiments. Tubercle bacilli were cultivated in a Tween[2]-albumin medium of the following composition: $Na_2HPO_4 \cdot 12H_2O$, 6.3 gm.; KH_2PO_4, 1 gm.; $MgSO_4 \cdot 7H_2O$, 0.02 gm.; $CaCl_2$, 0.0005 gm.; Tween 80, 0.2 ml.; bovine albumin (plasma fraction V), 1 gm.; NH_4Cl, 0.5 gm.; glucose, 10 gm.; distilled water, 1,000 ml. After five days of incubation at 37°C., the bacteria were collected by centrifugation, washed twice in a solution containing 0.01 per cent Tween and 0.1 per cent bovine albumin, and resuspended in a medium of the same composition except that no glucose was present. Aliquots of this suspension (5.4 ml.) were distributed into a series of screw-capped culture tubes. To one set of these tubes, isoniazid was added in a final concentration of 0.5 γ per ml. To another set the same amount of isoniazid and glucose, to constitute a final concentration of 1 per cent, was added. No additions were made to a third set. A total volume of 6 ml. was established in all tubes by the addition of distilled water. The inoculated tubes were incubated at 37°C. At various intervals, density readings were taken and colony counts were made, the latter by preparing tenfold dilutions in 0.1 per cent albumin and plating on oleic-acid–albumin agar and on oleic-acid–albumin agar in which 0.5 γ of isoniazid per ml. was incorporated. The latter medium was used in order to determine the number of isoniazid-resistant bacteria. The acid-fast property of the bacteria was also tested at various times by mixing loopfuls of culture with 10 per cent rabbit serum on a slide, fixing by brief flaming, and using the technique[3] of Aubert,[4] extending the time of staining to fifteen minutes.

The results of the colony counts in an experiment with the H37Rv strain are presented in table 1. It can be seen that the number of viable bacilli in the medium with isoniazid and glucose dropped after three days to $\frac{1}{500}$ of the original number and, after seven days, to less than $\frac{1}{1,000}$. After three weeks, the counts were again very high, but the organisms were now all isoniazid resistant, as indicated by the similar colony counts on the media

[1] Mackaness, G. B., and Smith, N.: Am. Rev. Tuberc., 1953, *67*, 322.

[2] Tween 80 is the proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, obtainable from the Atlas Powder Company, Wilmington, Delaware.

[3] Aubert, E.: Canad. J. Pub. Health, 1950, *41*, 31.

[4] In this method a special carbol fuchsin solution containing Tween is used. After staining at room temperature, the stain is washed off with water and the smear is decolorized with 5 per cent nitric acid for fifteen to thirty seconds and then for the same length of time with 70 per cent alcohol. The smear is washed and counterstained with methylene blue as usual.

with and without isoniazid. In the medium with isoniazid but without glucose, the bacteria lost their viability very slowly. After three weeks, one-seventh of the original number could still be cultivated. In the medium without either isoniazid or glucose, the bacteria remained perfectly viable throughout the whole period of the experiment.

TABLE 1

VIABILITY COUNTS OF TUBERCLE BACILLI (H37Rv) EXPOSED TO ISONIAZID IN THE PRESENCE AND IN THE ABSENCE OF GLUCOSE AS A SOURCE OF CARBON

The figures represent the number of colonies per ml. of a 10^{-4} dilution

	MODIFYING CONSTITUENTS OF THE MEDIUM:					
	Medium No. 1		Medium No. 2		Medium No. 3	
	NH_4Cl + Glucose − Isoniazid −		NH_4Cl + Glucose − Isoniazid +		NH_4Cl + Glucose + Isoniazid +	
DAYS OF INCUBATION BEFORE PLATING	TOTAL COUNT	ISONIAZID-RESISTANT	TOTAL COUNT	ISONIAZID-RESISTANT	TOTAL COUNT	ISONIAZID-RESISTANT
0	3,500	0	3,000	0	4,500	0
3	5,250	0	2,250	0	11	0
7	4,400	0	1,250	0	2.5	0.5
21	6,000	0	500	0	9,200	7,750

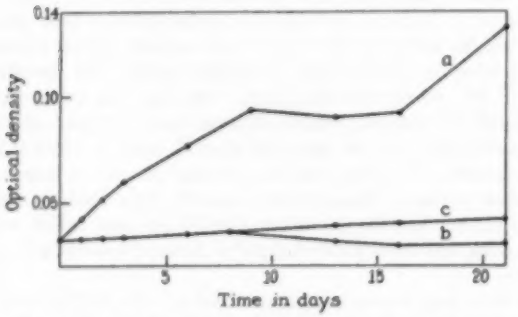

FIG. 1. Effect of isoniazid on the growth of *M. tuberculosis* (H37Rv) in Tween-albumin medium with and without glucose. The media contained NH_4Cl as the sole nitrogen source. *a*—Isoniazid, 0.5 γ per ml., and glucose, 10 mg. per ml., were added. *b*—Isoniazid, 0.5 γ per ml., was added alone. *c*—No additions were made.

It can be concluded from this and similar experiments that isoniazid has a strong bactericidal effect on tubercle bacilli only when these are in an environment which provides them with a carbon and energy source. The results of the density measurements (figure 1) indicate that the bacteria exposed to isoniazid in the presence of glucose proliferated in this medium for one and a half generations before their growth was arrested. After two weeks the growth of the isoniazid-resistant bacteria became visible. In the absence of glucose, some slow and sparse growth was observed, probably owing to the nutrient properties of Tween. This small amount of growth may explain the slight bactericidal

effect of isoniazid under these conditions and also the trace of lysis which occurred later. The observation that tubercle bacilli grow in a nutrient medium in the presence of isoniazid for a short period of time and for approximately one generation has been reported by Middlebrook,[5] by Barclay, Ebert, and Koch-Weser,[6] and by Mackaness and Smith.[1]

Isoniazid was seen to have a remarkable effect on the acid-fastness of the bacteria. In the medium with glucose and isoniazid, the bacteria lost their acid-fastness almost completely within two days. Acid-fast bacilli were found only rarely until the end of the second week of incubation. Thereafter, at the same time that the resistant organisms started growing, the number of acid-fast organisms increased progressively. The bacteria which were exposed to isoniazid in the absence of glucose retained throughout the experiment their ability to take the acid-fast stain intensely and homogeneously. Frequent beading of the acid-fast material in the bacterial cells was observed in the media lacking both glucose and isoniazid. Rapid loss of acid-fastness in young cultures of tubercle bacilli was described by Middlebrook[5] and by Rist and his collaborators.[7]

In summary: The effect of isoniazid on tubercle bacilli was studied in media with and without glucose as the only carbon source.

Isoniazid was rapidly bactericidal in the presence, but not in the absence, of glucose. In the presence of glucose, the bacteria proliferated for one and a half generations before their growth was arrested. They lost their acid-fastness nearly completely within two days. In the absence of glucose, there was no growth and no loss of acid-fastness of the bacteria. It is concluded that isoniazid acts on growing, but not on resting, tubercle bacilli.

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[8] Present address: National Jewish Hospital, 3800 East Colfax Avenue, Denver 6, Colorado.

Correspondence

PROCEDURE WITH NEGATIVE CULTURES FOR TUBERCLE BACILLI

To the Editor of the American Review of Tuberculosis:

In a letter I wrote on July 14, 1953, which was published in the September, 1953, issue of the AMERICAN REVIEW OF TUBERCULOSIS, I stated that it was my understanding that the Communicable Disease Center, Chamblee, Georgia, recommended the smearing of the surfaces of cultures negative for tubercle bacilli in order that positive cultures of bovine or dysgonic human tubercle bacilli would not be overlooked. I have since learned that my information was erroneous. The Tuberculosis Laboratories of the Communicable Disease Center neither follows nor recommends this procedure.

From other correspondence I have received on the subject, I find that the smearing of negative cultures is discouraged since the mere presence of acid-fast bacilli on a culture slant does not necessarily mean that the organisms are viable or virulent.

Sincerely yours,
CONSTANCE J. CONNORS

OHIO TUBERCULOSIS HOSPITAL
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November 6, 1953

Books

GREAT ADVENTURES IN MEDICINE. Edited by Samuel Rapport and Helen Wright, with an introduction by Detlov W. Bronk. Pp. 874, Dial Press, New York, 1952, Price, $5.00.

This book, intended for popular reading, is an anthology of the art and science of medicine. The editors have achieved much more than that. It will certainly be read with profit and interest by physicians. It has some of the features of Major's more extensive and professional *Classic Descriptions of Disease*. Furthermore, by their careful selections, systematic organization, and well-written orienting synopses the editors have produced a history of medicine for both lay and professional reading. The quality of high adventure in medicine, intentionally highlighted by the collection, cannot fail to be a source of pride to the medical reader and inspiration to young persons contemplating a medical career.

Beginning with the Hippocratic oath and the oath and prayer of Maimonides, the collection is arranged roughly in chronological order. The reader is exposed to the writings (in the original, translated when necessary, of course) of Hippocrates, Galen, Paré, Paracelsus, Sydenham, Hunter, Jenner, Laennec, Leeuewenhock, Lister, Pasteur, Bernard, Koch, Roentgen, Ross, Reed, and many others.

Seventeenth century diarist, John Aubrey, is represented by his account of the personality of his friend, William Harvey. Boccaccio describes the plague with the feeling of a first-hand observer. Shakespeare's description of the apothecary's shop in *Romeo and Juliet* and Dickens' Sairey Gamp, although fictional, are certainly valid inclusions. LeSage's description of Doctor Sangrada in *The Adventures of Gil Blas of Santillane* falls in the same category. John Brown's touching *Rab and His Friends* should certainly not have been omitted. Even Ben Franklin's observations on lead poisoning and his description of bifocal spectacles are included.

Writings for popular consumption, favorites in the 1930's, by physicians Carrel, Finney, Heiser, Hertzler, Schweitzer, Zinnser, and others are well represented. The contemporary era is interpreted by persons such as Cornelius P. Rhoades, René Dubos, Alexander Fleming, William C. Meninger, Wendell Stanley, and others.

This book is wholeheartedly recommended.

VICTOR A. MCKUSICK
Baltimore, Maryland

THE THORACIC SURGICAL PATIENT. By Lew A. Hochberg. Pp. 365, Grune & Stratton, Inc., New York, 1952. Price, $8.75.

Condensed into this 350-page, manual-sized volume are this well-known author's views on the following subjects: the physiology of the respiratory and cardiovascular systems; endoscopy; anesthesiology; chest injuries; surgery of the chest wall, esophagus, mediastinum, heart, lungs, and diaphragm; collapse therapy; and patient rehabilitation. As can be imagined, an almost outline form is required to encompass these fields. Each of these subjects may be found discussed in a more complete and a more fully illustrated form in other texts. The virtue of this volumn is that it provides a broad perspective of the entire field which can be acquired rapidly and provides a framework for more careful consideration of each of these major subjects.

DANIEL M. HAYS
New York, New York

THE EPIDEMIOLOGY OF HEALTH. Edited by Iago Galdston. Pp. 197, Health Education Council, New York and Minneapolis, 1953, Price, $4.00.

This publication arose out of The Eleventh Annual Eastern States Health Education Conference. The 15 chapters by various contributors deal with epidemiology and preventive medicine in selected areas of health and disease. The author of the three chapters which provide the nucleus of the text is John E. Gordon, Professor of Epidemiology at The Harvard School of Public Health. He applies himself to a compact review of the history of epidemiology, culminating in an appeal for adherence to the holistic ecologic view of the phenomena of disease and health, and calling for a concerted effort to identify and measure factors determining "gradients of health." The Surgeon General of the Army tells of the efforts of his organization to equilibrate man with his environment. Alton S. Pope discusses epidemiologic aspects of tuberculosis. Other contributors treat the subjects of mental health, nutrition, health in industry, health in old age, and certain other phases of preventive medicine and public health.

The book is disappointing in its meager content of new ideas or concise information about "the epidemiology of health." The title is misleading. However, with a modicum of breadth and depth, the elements of epidemiology and their projection in the prevention of disease and promotion of health are set forth by men who know their fields. The health educator should find the book useful and stimulating.

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BOOKS RECEIVED

PRINCIPLES OF MICROBIOLOGY. By Walter W. Krueger. Pp. 648, with illustrations, W. B. Saunders Company, Philadelphia and London, 1953, Price, $5.50.

BACTERIAL GENETICS. By Werner Braun. Pp. 238, with illustrations, W. B. Saunders Company, 1953, Price, $6.50.

STUDIER ÖVER UROGENITALTUBERKULOSENS BEHANDLUNG. By Karl Ola F. Obrant. Pp. 159, Fran Kirurgiska Kliniken I Vid Sahlgrenska Sjukhuset, Göteborg, 1953.

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Detroit

MINNESOTA

R. W. Backus, M.D.
Nopeming Sanatorium
Nopeming

MISSISSIPPI

Robert E. Schwartz, M.D.
990 Hardy Street
Hattiesburg

MISSOURI

Charles Brasher, M.D.
Missouri State Hospital
Mt. Vernon

MONTANA

F. I. Terrill, M.D.
State Tuberculosis Sanatorium
R. F. D. #1
Deer Lodge

NEBRASKA

J. F. Gardiner, M.D.
628 Medical Arts Building
Omaha 2

NEVADA

C. Robert Locke, M.D.
Chesnut and Fifth
Reno

NEW HAMPSHIRE

Francis J. Kasheta, M.D.
New Hampshire State Sanatorium
Glencliff

NEW JERSEY

Harold S. Hatch, M.D.
Shonghum Mountain Sanatorium
Morristown

NEW MEXICO

J. Gordon Strance, M.D.
Medical Arts Square, NE
Albuquerque

NEW YORK

James M. Blake, M.D.
Glenridge Sanatorium
Schenectady

NORTH CAROLINA

David T. Smith, M.D.
Duke University Medical School
Durham

NORTH DAKOTA

Paul Breslich, M.D.
North West Clinic
Minot

OHIO

Herman J. Nimitz, M.D.
Dunham Hospital
Cincinnati

OKLAHOMA

R. M. Shepard, M.D.
306 Medical Arts Building
Tulsa 3

OREGON

James T. Speros, M.D.
University State TB Hospital
9181 S. W. Sam Jackson Road
Portland 1

PENNSYLVANIA

Robert V. Cohen, M.D.
255 S. 17 Street
Philadelphia 3

RHODE ISLAND

William B. O'Brien, M.D.
State Sanatorium
Wallum Lake

SOUTH CAROLINA

Rudolph Farmer, M.D.
South Carolina Sanatorium
State Park

SOUTH DAKOTA

William L. Meyer, M.D.
South Dakota State Sanatorium
Sanator

TENNESSEE

R. B. Turnbull, M.D.
TB Field Service
West Tennessee District
842 Jefferson Avenue
Memphis

TEXAS

John W. Middleton, M.D.
5018 Sherman
Galveston

UTAH

George A. Spendlove, M.D.
State Capitol Building
Salt Lake City

VERMONT

Louis Benson, M.D.
Vermont Sanatorium
Pittsford

VIRGINIA

Edward S. Ray, M.D.
Medical College of Virginia
Richmond

WASHINGTON

Daniel Zahn, M.D.
1704 East 150 Street
Seattle 55

WEST VIRGINIA

George F. Evans, M.D.
122 South Sixth Street
Clarksburg

WISCONSIN

Helen Dickie, M.D.
1300 University Avenue
Madison 6

WYOMING

Russell H. Kanable, M.D.
Wyoming State Sanatorium
Basin

BRITISH COLUMBIA

Gordon F. Kincade, M.D.
2647 Willow Street
Vancouver

Present Objectives and Policies of the American Trudeau Society in the Field of Medical Education and the Role and Responsibility of the Committee on Medical Education.[1]

The role of the Committee and its subcommittees is directly concerned with a major objective of the Society, namely, the CONTINUING IMPROVEMENT OF MEDICAL EDUCATION IN THE FIELD OF CHEST DISEASES. The Committee has the following responsibilities:

1. Selecting and defining objectives of medical education in our field
2. Evaluating current programs
3. Developing and recommending changes in existing programs

Our interests and efforts should be concerned with instruction and training at all levels:

1. The undergraduate
2. The internship and resident
3. The fellowship
4. The postgraduate

Guiding Principles

Certain fundamental principles and considerations should serve to guide and direct our endeavors in the four categories mentioned. These are:

1. The practice of scientific medicine and the pursuit of useful and productive research in diseases of the chest are inherently and inseparably related to sound preparation in the basic sciences, in the broad field of internal medicine, and in the acquisition of special knowledge, skills, and techniques in this field.

2. Medical education of a high order is a continuing process; hence the necessity of competent instruction and training at the undergraduate, the graduate, and postgraduate levels.

Objectives

Our major objectives may be considered as primary and secondary. The primary objective should be to interest *all* medical schools and students in this segment of internal medicine. The secondary objective should be the encouragement of a limited number of promising young physicians to acquire special knowledge, understanding, and skills in this group of diseases after the completion of their training in the broader field of internal medicine. Our primary aims can be accomplished by proper stimulation and instruction at the undergraduate level; our secondary objectives, as a result of more prolonged and intensive training at the resident, fellowship, and postgraduate levels. The primary objective is largely the responsibility of medical schools and their faculties; the secondary objective is that of teaching hospitals, research laboratories, special institutes, and certain tuberculosis hospitals and chest services.

It should be the continuing duty and responsibility of our Society, working through its Medical Education Committee and its several subcommittees, to make every effort to encourage medical schools, teaching hospitals, research laboratories, and tuberculosis hospitals to carry out their educational responsibilities in this field. The achievement of our purposes will remain complex and difficult since competition is becoming increasingly keen between all teaching departments for more time, more teaching personnel, more teaching funds and, to some extent, more facilities. Since the curriculum time is sharply limited, the physical facilities and clinical material, adequate to fairly adequate in most schools and

[1] The objectives and recommendations as expressed in this report concerning medical education were accepted and became the policy of the Society at the annual meeting of the Council in Los Angeles, May 17, 1953.

teaching hospitals, it appears that the Committee might best achieve its major objectives (*a*) *by assisting medical schools to attract additional full or part-time teachers to this field,* (*b*) *by aiding the schools to obtain additional funds for these teachers,* (*c*) *by stimulating greater interest in and enlarging and improving our fellowship program.*

Greater interest in the undergraduate teaching program in chest diseases cannot be accomplished without general acceptance of the sound philosophy that chest diseases can be properly taught only as a segment of the whole field of internal medicine in relationship to the basic sciences and in an environment of scientific research. A competent internist-teacher with special training and a major interest in chest diseases should organize and correlate the teaching in this field in every medical school. It is believed that this philosophy should become the basic policy of the Society. If this philosophy and policy are officially adopted by the Society, a program directed toward their fulfillment should be put into operation. (This recommendation was accepted by the ATS Council and, therefore, becomes the official policy of the Society.)

Steps toward the achievement of these goals should be taken in an orderly manner and according to well-conceived plans. The approach to medical schools should be on a personal and individual basis. Following a thorough evaluation of the present study of the status of undergraduate teaching in chest diseases, an early and probably the next step by the Committee might be to consider with the Director of Medical Education the advisability of approaching the professors of medicine and deans of those schools having the greatest need for improvement in undergraduate instruction in chest diseases. The approach would be made primarily to discuss the particular problems of the individual school. The Director could also acquaint the professor of medicine with the policy and activities of the Society concerning the need of improving instruction and training in chest diseases. Should opportunity present itself, the Director might also wish to inform the medical school concerning the Committee's findings relative to the different methods and quality of teaching in this field in general. The Director might also wish to mention the possibility of assistance from the National Tuberculosis Association, the American Trudeau Society, and the constituent tuberculosis associations in the area of the medical school provided, of course, the school is willing to make its maximum contribution. Subsequent cooperation between the medical school, the Committee, and related organizations would depend upon the results of the initial conference. *It is further recommended that the Director of Medical Education, after consultation with the chairman of the parent committee and regional subcommittees and, preferably, in conjunction with the Field or Executive Secretary, visit all medical schools or, at least, those thought to be most in need of improving instruction in chest diseases.*

Studies now well along should indicate those schools doing adequate to superior teaching and those doing relatively inferior or limited teaching in the field. Available information shows that some schools are doing outstanding teaching in this field; and others, limited or inferior teaching. Many are doing a much better job than is generally known. The data also suggest that improvements can best be made in the *quality* rather than the *quantity* of teaching.

It is also recommended that *the Committee and the Society encourage its members to become more closely and better integrated with, and more active in, the broad field of internal medicine academically and in practice. The Committee, its regional subcommittees especially, and its state representatives should make every effort to have members of the Society participate in scientific programs of organized medicine at all levels—national, regional, state, and local. In this way those specializing in the field can exert a greater educational influence in the broader field of internal medicine.*

Finally, the Committee, its subcommittees, the Society, and the NTA should continue

to emphasize the fact that optimum tuberculosis control can be attained only by gaining and holding the interest of *all* physicians in diseases of the chest and by retaining the interest and close cooperation of those specializing in the field. This should be emphasized not only by the ATS but more particularly by the NTA and its constituent associations until *medical education* has become as much a part of the antituberculosis movement as *health education*.

Postgraduate Courses

A few brief comments regarding past efforts in this field may suggest possible leads for the future. Activities by the Committee and its subcommittees in the postgraduate field have consisted mainly of (*a*) the combined (medical, surgical, and laboratory) refresher courses usually of a week's duration, (*b*) courses on cardiopulmonary function, and (*c*) Pembine, Koppa, or case conferences. There appears to be more real interest in, and a greater demand for, courses on cardiopulmonary function and conferences of the Pembine, Koppa, or case type than the usual refresher course. *It is recommended, therefore, that all regional subcommittees get together at the time of the annual meeting of the Society and at other times, if necessary, to discuss plans regarding postgraduate courses and conferences in their areas during the ensuing year.*

The Fellowship Program and Grants to Medical Schools

Despite the fact that the fellowship program is still in its infancy, it has shown, during recent months, increasing vigor and signs of becoming one of the most fruitful activities of the Society in the field of medical education. Ten Fellows have filed applications for fellowships during recent months. This is in sharp contrast to three applications filed during the past fiscal year. This increase in interest is apparently related to a letter sent to medical schools and teaching hospitals calling attention to the availability of a limited number of fellowships. *It is recommended that similar letters of notification be sent out periodically if efforts to recruit qualified physicians to this field are to succeed.*

With fellowship stipends ranging from $2,400 to $3,200, it is readily apparent that a fellowship budget of $8,000, even if matched with funds from state and local associations, is totally inadequate if the fellowship program is to expand in relation to the obvious need of continuous recruitment of promising physicians to this field. *It is therefore recommended that the Committee on Medical Education and the Fellowship Committee give consideration to the advisability of requesting a larger budget item for the fellowship program in the future.* A minimum of $25,000, with even further assistance from constituent associations, will probably prove inadequate.

The following are also recommended: That the Director of Medical Education and the Chairman of the parent committee in cooperation with the chairmen of the Fellowship and Regional Subcommittees, and their NCTW representatives, the tuberculosis association secretaries and, possibly, the state Advisory Board members develop suitable plans and procedures for the purpose of keeping in constant touch with officers and executives of local and state tuberculosis associations and Trudeau societies in order to acquaint, stimulate, and promote greater interest in the Medical Education program on the part of responsible individuals at the local level; that written requests be made to the proper officers and executives of state and local tuberculosis associations asking that their boards of directors consider the advisability of budgeting a limited amount of funds for (a) the specific purpose of teaching-resident fellowships for candidates within their states and localities, and (b) for limited teaching grants to needy medical schools within their respective areas. It is further recommended that the availability of fellowships and limited grants to faculty members teaching chest diseases be given adequate publicity through various media, including letters to medical schools, teaching hospitals, and tuberculosis hospitals within the state and locality concerned.

Teaching Resident Fellowships

It is also recommended that the Teaching-Resident Fellowship Subcommittee review and appraise all fellowship applications, whether the fellowship is to be financed jointly or on the local or state level and, if requested, advise regarding the possible placement of suitable candidates. It is further recommended after receipt, review, and tentative approval of applications that the Teaching-Resident Fellowship Subcommittee, through the Director of Medical Education, reach the proper local and state tuberculosis association authorities with the view of determining whether or not the local or state association would be willing to finance the fellowship jointly or alone. If the local or state association is unable to finance the fellowship alone, it is recommended that efforts be made to arrange a cooperative or joint fellowship; the grant to be shared by the local, state, and the NTA.

Promotion of the idea of better medical education in the field of chest diseases and the assistance of the Field or Executive Secretary through personal contacts with officers and board members of local and state tuberculosis associations, regional and state Trudeau societies should be of the greatest value in this and other cooperative activities. *It is recommended that a very significant part of the Executive Secretary's time be devoted to the activities of the Committee on Medical Education and its several subcommittees.* The Division of Medical Education could effectively use all of its time acquainting the local and state tuberculosis associations and the state regional Trudeau groups with the official policy and objectives of the Society in matters of medical education. Once the "cooperative" idea of sharing in medical education becomes generally known, it is hoped that it may become "communicable" if not outright "contagious." It is predicated that the idea will become at least contagious and beneficially chronic if the germ is widely and effectively disseminated and the soil properly fertilized and tilled by the parent committee, regional and other subcommittees, the Director of Medical Education, and the Executive Secretary. Should this expectation be realized only in part and isolated Fellows appear, say, a Fellow-a-state-a-year, this would quadruple the present fellowship program. All and more could be effectively used in the achievement of our major objectives, namely:

1. Improvement of medical education and training in chest diseases at all levels
2. Wider participation of the medical profession, its local, state and national societies in the field of chest diseases
3. The practice of modern and scientific medicine in this field
4. More effective tuberculosis control

Regional Subcommittees

North Eastern Region

Connecticut	New Jersey
Delaware	New York
Maine	Pennsylvania
Maryland	Rhode Island
Massachusetts	Vermont
New Hampshire	District of Columbia

South Eastern Region

Alabama	North Carolina
Florida	South Carolina
Georgia	Tennessee
Kentucky	Virginia
Mississippi	West Virginia

North Central Region

Illinois	Missouri
Indiana	Nebraska
Iowa	North Dakota
Kansas	Ohio
Michigan	South Dakota
Minnesota	Wisconsin

South Central Region

Arkansas
Colorado
Louisiana
New Mexico
Oklahoma
Texas

North Western Region

Idaho
Montana
Oregon
Washington
Wyoming

South Western Region

Arizona
California
Nevada
Utah

Respectfully submitted,

J. Burns Amberson
Katharine R. Boucot
Robert H. Browning
†William L. Cooke
John Deitrick
†H. Corwin Hinshaw
†Sydney Jacobs
Daniel E. Jenkins
†William M. M. Kirby
John A. Louis
Richard L. Riley
John H. Skavlem
†William B. Tucker
†Edward J. Welch
Clarence A. Wicks

H. McLeod Riggins, *Chairman*

---

† Ex-officio members

NOTES

TELECOLOR CLINICS

The American Cancer Society, in conjunction with the facilities of the Columbia Broadcasting System TV Network, will produce during 1953–1954 a series of closed-circuit television programs for doctors in general practice.

The long-range objective of this project is to enlarge the pattern of nation-wide post-graduate medical education by inaugurating a pilot project of color television clinical presentations oriented to county medical societies. The immediate objective is to improve cancer cure rates by making available to the general practitioner knowledge of the most effective techniques in diagnosing and treating early cancer.

The program content will be governed by the following objectives:—

1. To stimulate among general practitioners, who see cancer first, *a recognition of the importance of their role* in determining the outcome of cancer.
2. To enhance the effectiveness of the practitioner in cancer control by:—
   (a) increasing his knowledge of early cancer,
   (b) demonstrating the indications for and the techniques of diagnostic procedures,
   (c) giving him a firm basis for deciding critically where to refer the patient, should specialist care be required.
3. To show methods and techniques of treatment and to analyze the results of such treatment.
4. To promulgate knowledge of research advances and of subjects under investigation.

There will be a series of thirty, one-hour closed-circuit Color Television broadcasts which will be viewed by practitioners in six major cities in the northeast—Boston, Philadelphia, Pittsburgh, Detroit, Toledo, and New York—with the possibility that other cities will be added as the series progresses. All programs will originate in New York, from the Columbia-Presbyterian Medical Center and from the Memorial Center. The tentative starting date for the series is Wednesday, October 21, 5:00 to 6:00 p.m., from a studio in Frances Delafield Hospital at Columbia. Programs will be broadcast on alternate Wednesdays up to December 2, after which they will be presented weekly.

In the New York area, the receiver will be located at The New York Academy of Medicine (Hosack Hall).

TELEVISION SCHEDULE

MEMORIAL CENTER

Preventive Medicine

Department	*Date*		*Title*
Emerson Day, M.D. Director, Strang Clinic	2-24-54	Emerson Day, M.D.	Cancer Detection
Surgery Henry T. Randall, M.D. Clinical Director Chief, Department of Surgery			
Head and Neck Service	3- 3-54	Hayes E. Martin, M.D. Attending Surgeon	Head and Neck Cancer
Breast Service	3-10-54	Norman E. Treves, M.D. Attending Surgeon	Hormone Therapy in Inoperable and Recurrent Breast Cancer
Thoracic Service	3-17-54	William L. Watson, M.D. Attending Surgeon	Cancer of the Lung
Gastric Service	3-24-54	George T. Pack, M.D. Attending Surgeon	Significance of Indigestion
Rectal and Colon Service	3-31-54	George E. Binkley, M.D. Attending Surgeon	Advances in Control of Cancer of Colon and Rectum
Gynecology Service	4- 7-54	Alexander Brunschwig, M.D. Attending Surgeon	Treatment of Recurrent Cancer of the Cervix
Urological Service	4-14-54	Willet E. Whitmore, M.D. Attending Surgeon	Cancer of the Genito-Urinary Tract
Bone Service	4-21-54	Bradley E. Coley, M.D. Attending Surgeon	Bone Tumors
Surgery Mixed Tumor	4-28-54	George T. Pack, M.D. Attending Surgeon	Melanoma

Medicine

Department	*Date*		*Title*
Rulon W. Rawson, M.D. Lloyd F. Craver, M.D. Co-Chiefs			
Medical Neoplasia Service	5- 5-54	Lloyd F. Craver, M.D. Attending Physician	Lymphoma and Leukemia
Pediatric Service	5-12-54	Harold W. Dargeon, M.D. Attending Pediatrician	Tumors of Childhood
General Medical Service	5-19-54	Rulon W. Rawson, M.D. Attending Physician	Hormonal and Chemical Treatment of Cancer
Medical Service	5-26-54	Raymond Houde, M.D. Asst. Attending Physician	Treatment of Patients with Advanced Cancer
Psychiatry			
		Arthur M. Sutherland, M.D. Assoc. Attending Physician & Psychiatrist	Psychiatry and Analgesia
Research			
C. P. Rhoads, M.D. Scientific Director Memorial Center Director, Sloan Kettering Institute	6- 2-54	C. P. Rhoads, M.D.	Frontiers of Research

COLUMBIA-PRESBYTERIAN MEDICAL CENTER

Date	*Representative*	*Title*
1-6-54	Dr. Howard C. Taylor, Jr.	The Diagnosis and Treatment of Uterine Cancer
1-13-54	Dr. Arthur Purdy Stout	Sarcoma of Soft Parts
1-20-54	Dr. Maurice Lenz Dr. Ernest Daland, Boston	Cancer of the Oral Cavity
1-27-54	Dr. Maurice Lenz	Cancer of the Larynx and Hypopharynx
	Dr. William B. Parsons	Cancer of the Thyroid
2-3-54	Dr. Arthur Purdy Stout Dr. Thomas Stevenson Dr. Maurice Lenz	Cancer of the Skin
	Dr. Lawrence Pool Dr. Thomas Bridges	Cancer of the Central Nervous System
2-10-54	Dr. Alfred Gellhorn Dr. Ruth Gutman	Lymphomas and Leukemias
2-17-54	Dr. Alfred Gellhorn Dr. Maurice Lenz Dr. Thomas Bridges	The Management of Advanced Cancer

Location of Giant Screen Receivers

New York, N. Y.—Hosack Hall
New York Academy of Medicine
2 East 103 Street
Boston, Mass.—Auditorium
Children's Cancer Research Foundation
35 Binney Street
Toledo, Ohio—Auditorium
Academy of Medicine Bldg.
3101 Collingwood Blvd.
Philadelphia, Pa.—WCAU Auditorium
City & Monument Aves.
Pittsburgh, Pa.—Mellon Institute
4400 Fifth Ave.
Detroit, Mich.—Auditorium
Masonic Temple
500 Temple Ave.
Dearborn, Mich.—Ford Rotunda
Schaefer Highway & Rotunda Drive

Further information may be obtained from the American Cancer Society, Inc., 47 Beaver Street, New York, 4, N. Y.

PHTHISIOLOGIST WANTED IN KOREA

Several Protestant mission boards are planning a coordinated preventive and curative tuberculosis program for Korea, which will consist of the establishment of a training center at the Severance Medical College in Seoul, the strengthening with personnel, equipment, and funds of the antituberculosis services of the mission institutions, and the organization of preventive measures. The missions are in urgent need of an experienced phthisiologist, who should be a member of the Protestant Church and willing to serve on a modest salary for a period of at least three years, to take charge of this project as director. Further information can be obtained from Douglas N. Forman, M.D., Secretary, Christian Medical Council for Overseas Work, Room 1111, 156 Fifth Avenue, New York 10, N. Y.

AWARD OF THE DEARHOLT MEDAL

The Dearholt Medal was awarded to William H. Feldman, D.V.M., of Rochester, Minnesota, for his outstanding work done in the development of streptomycin.

TEACHING-RESIDENT FELLOWSHIPS

The American Trudeau Society, medical section of the National Tuberculosis Association, provides a limited number of fellowships to promote the training of clinicians, medical teachers, and administrators in the field of tuberculosis and related pulmonary diseases. The awards are open to citizens of the United States for work within this country. Preference is given to candidates not more than thirty years of age who have the degree of Doctor of Medicine.

Awards are made for graduate study in internal medicine, with emphasis on diseases of the chest, in an approved hospital. Fellows are expected to assume some responsibility for the teaching of chest diseases to undergraduate medical students. The American Board of Internal Medicine will accept one such year as a part of the prerequisite training for certification.

Stipends are determined by individual circumstances and may vary from $2400 to $3200 per annum, paid on a monthly basis. They are made for one year. Not more than two renewals will be considered. Fellowship applications are considered at meetings of the Committee on Medical Education of the American Trudeau Society in October and April or May; to receive consideration at these meetings they must be received by September 1 or April 1. Appointments may begin on any date determined by the Board at the convenience of the applicant, who may elect the hospital in which he wishes to study and the staff member who will supervise his work.

Further particulars concerning these fellowships may be obtained on request.

Address communications to The Director of Medical Education, American Trudeau Society, Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia 47, Pennsylvania.

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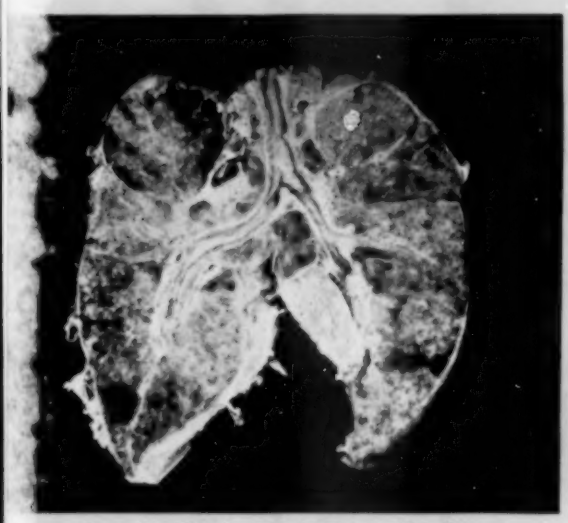

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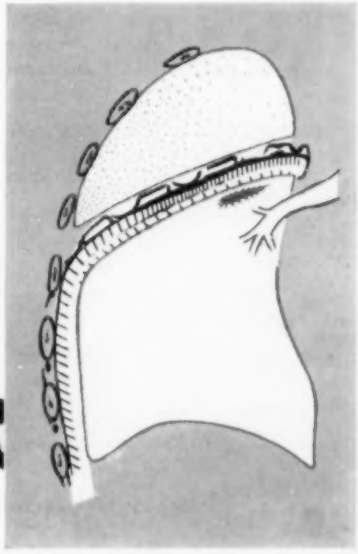

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American College of Chest Physicians—**NONTUBERCULOUS DISEASES OF THE CHEST.** Edited by A. L. Banyai (1st Ed. pub. '53), about 1120 pp., about 220 il. Cloth, about $18.50

William F. Dres and Anatole Andrejew—**THE METABOLISM OF THE TUBERCLE BACILLUS** (1st Ed. pub. '53), 470 pp., 24 il., Cloth, $12.50

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K. N. Irvine—**B.C.G. VACCINATION IN THEORY AND PRACTICE** (1st Ed. pub. '49), 142 pp. Cloth, $4.00

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